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CONTENTS OF VOL. 213

ORIGINAL ARTICLES

No. 1—JANUARY

The Migrainous Personality and Constitution. The Essential Features of the Disease: A Study of 500 Cases. By WALTER C. ALVAREZ, M.D.	1
Fatal Infection With Poliomyelitis Virus in a Laboratory Technician. Isolation of Virus From Lymph Nodes. By HERBERT A. WENNER, M.D., and JOHN R. PAUL, M.D. . .	9
Gynecomastia Due to Malnutrition. I. Clinical Studies. By GERALD KLATSKIN, M.D., WILLIAM T. SALTER, M.D., and FRANCES D. HUMM, PH.D.	19
Gynecomastia Due to Malnutrition. II. Endocrine Studies. By WILLIAM T. SALTER, M.D., GERALD KLATSKIN, M.D., and FRANCES D. HUMM, PH.D.	31
Mild Rheumatic Reaction in Coast Guard Recruits. By H. POLIAKOFF, M.D.	37
Blood Pressure Studies in 100 Cases of Coronary Occlusion With Myocardial Infarction. By MAJ. WILLIAM N. CHAMBERS, M.C., A.U.S.	40
Specific Dynamic Action as a Means of Augmenting Peripheral Blood Flow. Use of Amino-acetic Acid. By RICHARD GUBNER, M.D., F.A.C.P., JOSEPH R. DI PALMA, M.D., and ELIZABETH MOORE, A.B.	46
An Evaluation of Immune Serum Globulin as a Prophylactic Agent Against Homologous Serum Hepatitis. By COL. GARFIELD G. DUNCAN, M.C., A.U.S., LT. COL. HENRY A. CHRISTIAN, M.C., A.U.S., JOSEPH STOKES, JR., M.D., CAPT. WILLIAM F. REXER, M.C., A.U.S., CAPT. JOSEPH T. NICHOLSON, M.C., A.U.S., and LT. A. EDGAR, M.C., A.U.S.	53
Histamine Antagonists. IV. Pyridil-N'benzyl-N-dimethylethylenediamine (Pyribenzamine) in Symptomatic Treatment of Allergic Manifestations. By SAMUEL M. FEINBERG, M.D., and SIDNEY FRIEDLAENDER, M.D.	58
The Pathology of Experimental Frostbite. By MAJ. NATHAN B. FRIEDMAN, M.C., A.U.S., KURT LANGE, M.D., and DAVID WEINER, M.D.	61
Use of Posterior Pituitary Extract (Pituitrin) to Measure Renal Function. By S. F. HORNE, M.D., and LESLIE M. MORRIS, M.D.	68
Thiouracil in Thyrotoxicosis—Results of Prolonged Treatment in 35 Cases. By EDWARD ROSE, M.D., and JEANNETTE McCONNELL, M.D.	74
The Relationship of Bromsulphalein Retention to the Fever of Natural P. Falciparum Malaria. By MAJ. THOMAS E. MACHELLA, M.C. With the technical assistance of RALPH FINE, T/5, and DAVID F. BURGOON, 2ND LT., SN.C.	81
Rheumatoid Arthritis. IV. Hemolytic Streptococcus Precipitin Reactions. By ALLAN D. WALLIS, M.D.	87
Rheumatoid Arthritis. V. The Agglutination of Hemolytic Streptococci. By ALLAN D. WALLIS, M.D.	94

No. 2—FEBRUARY

A Study of an Outbreak of Influenza B in Rochester, New York. By ROBERT A. BRUCE, M.D., and HOWARD B. SLAVIN, M.D.	129
Relative Clinical and Hematologic Effects of Concentrated Liver Extract, Synthetic Folic Acid and Synthetic 5-methyl Uracil in the Treatment of Macrocytic Anemias in Relapse. By WALTER B. FROMMEYER, JR., M.D., and TOM D. SPIES, M.D.	135

Clinical Significance of Hyperbilirubinemia Due to Nicotinic Acid. By L. MARIONI, M.D., M. STEFANINI, M.D., and P. BRAMANTE, M.D.	150
Atypical Anemia, With Spherocytes and Target Cells Coexisting in the Blood. By G. DISCOMBE, M.B., B.S., B.Sc. (LOND.), and G. WATKINSON, M.D., M.R.C.P.	153
Nitrogen Balance and Blood Volume Studies in Man During and Following Repeated Plasma Transfusions. By FRIEDA L. MEYER, Ph.D., JOHN WINSLOW HINSHFELD, M.D., WILLIAM E. ABBOTT, M.D., MATTHEW A. PILLING, M.D., HAROLD H. WILLIAMS, Ph.D., and ALLEN J. RICHARDS, B.S.	160
Partial Maturation of Leukemic Myeloblasts Following Fresh Plasma Transfusions. By JOSEPH L. SCHWIND, Ph.D.	170
Gynecomastia Associated With Vitamin Deficiency Disease. By RALPH E. HIBBS, M.D.	176
The Effect of Patent Ductus Arteriosus on Body Growth. By WILLIAM B. PORTER, M.D.	178
Heberden's Nodes. VI. The Effect of Nerve Injury Upon the Formation of Degenerative Joint Disease of the Fingers. By ROBERT M. STECHER, M.D., and LOUIS J. KARNOSH, M.D.	181
The Indications for Irradiation of the Pituitary Gland in Patients With Arterial Hypertension. By EUGENE P. PENDERGRASS, M.D., JOHN Q. GRIFFITH, JR., M.D., NICHOLAS PADIS, M.D., and ROBERT P. BANDEN, M.D.	192
Further Studies on the Correlation of Chemical Structure and Antithyroid Effect. By ROBERT H. WILLIAMS, M.D., and GLORIA A. KAY, B.S. Assisted by BABETTE SOLOMON, B.A.	198
Posthypoglycemic Encephalopathy. Case Reports. By GEORGE M. JONES, M.D.	206
Plasma Proteins. II. Alteration in Alloxan Diabetic Rabbits Especially in Relation to Ocular Damage. By LENA A. LEWIS, Ph.D., JACOB MOSES, M.D., and R. W. SCHNEIDER, M.D.	211
A Routine Method for the Rapid Determination of Susceptibility to Penicillin and Other Antibiotics. By AMEDEO BONDI, JR., Ph.D., CARLE H. SPAULDING, Ph.D., DOROTHY E. SMITH, B.S., and CATHERINE C. DIETZ, M.S.	221
Thrombophlebitis on the Medical Service of a General Hospital. By HORACE H. HODGES, CAPTAIN, M.C., A.U.S., and NORMAN E. FREEMAN, MAJOR, M.C., A.U.S.	226

Insensitivity to Epinephrine in a Patient With a Functioning Tumor of the Adrenal Medulla. By ROBERT L. MAYOCK, M.D., and EDWARD ROSE, M.D.	324
Increased Reactivity Caused by Adrenalin. By D. EWEN CAMERON, M.D.	331
Thiamine Circulation Time. By ARTHUR RUSKIN, M.D., and GEORGE M. DECHERD, JR., M.D.	337
The Electrocardiographic Changes Caused by Hyperventilation. By DAVID SCHERF, M.D., F.A.C.P., and MILTON SCHLACHMAN, M.D.	342
Injectational Treatment of Internal Hemorrhoids. By ROBERT TURELL, M.D.	350
Complications of Mumps. By JOSEPH HUMPHRIES, M.D.	354
Further Report on the Use of Bismuth Sodium Tartrate Intravenously in the Treatment of 203 Additional Patients With Tularemia. By WILL W. JACKSON, M.D.	358

No. 4—APRIL

Clinical Features of Patent Ductus Arteriosus With Special Reference to Cardiac Murmurs. By S. A. LEVINE, M.D., and A. E. GEREMIA, M.D.	385
Infectious Hepatitis: Clinical and Laboratory Features of 295 Cases. By HYMAN J. ZIMMER- MAN, CAPT., M.C., CHARLES F. LOWRY, LT. COL., M.C., KAHN UYEBAMA, MAJOR, M.C., and RAYMOND REISER, 1ST LT., SAN. C., A.U.S.	395
Liver Dysfunction in Rheumatic Heart Disease. Preliminary Report. By R. W. KISSANE, M.D., R. S. FIDLER, M.D., and THOMAS E. CLARK, M.D.	410
The Treatment of Pneumococcic Pneumonia With Oral and Intramuscular Penicillin. By HARRY F. DOWLING, M.D., GEORGINE ROTMAN KAVKA, M.D., HUGH H. HUSSEY, M.D., and HAROLD L. HIRSH, M.D.	413
Some Pharmacological and Clinical Experiences With Dimethylaminoethyl Benzhydryl Ether Hydrochloride (Benadryl). By THOMAS H. MCGAVACK, HERBERT ELIAS and LINN J. BOYD	418
The Intravenous Use of Human Ascitic Fluid in Shock, Nephrosis and Allied Conditions. By RICHARD D. MOLINA, M.D., HERMOGENES A. SANTOS, M.D., and MARIANO M. ALIMURUNG, M.D.	435
Renal Excretory Function and Diet in Diabetes Insipidus. By SAMUEL B. BEASER, M.D.	441
Observations on the Treatment of Carcinoma of the Prostate by Orchidectomy. By ERNEST K. LANDSTEINER, M.D., and HATHORN P. BROWN, M.D.	450
The Femoral Bone Marrow Cells of the Albino Rat. By MILDRED VOGEL, M.D.	456
Postpartum Blood: Its Clotting Mechanism and Relationship to the Peripheral Blood Picture. By ALLAN C. BARNES, M.S., M.D.	463
The Effect of Circulatory Factors on the Bromsulphalein Test in Liver Disease. By NATHAN BLUMBERG, M.D., F.A.C.P., and EUGENE M. SCHLOSS, M.D.	470
Menopausal Hypertension: A Critical Study. By R. D. TAYLOR, M.D., A. C. CORCORAN, M.D., and IRVINE H. PAGE, M.D.	475
Amylase Levels During Mumps. The Findings in Blood and Saliva. By IRVING J. WOL- MAN, M.D., BARNETT EVANS, C.PH.M., SIGMUND LASKER, PH.M.1/C, and KENNETH JAEGER, PH.M.3/C	477
The Failure of Massive Salicylate Therapy to Suppress the Inflammatory Reaction in Rheumatic Fever. By T. N. HARRIS, M.D.	482
Changes in Personality Appraisal Associated With a Restricted Intake of B Vitamins and Protein. By CHARLES R. HENDERSON, NORMAN C. WHEELER, HOWARD C. JOHNSON, ROBERT C. COGSWELL, JR., GEORGE H. BERRYMAN, ANDREW C. IVY, THEODORE E. FRIEDEMANN and JOHN B. YOUNANS	488

No. 5—MAY

Studies in the Oral Administration of Penicillin. I. Assays of Various Preparations and the Determination of the Effective Therapeutic Dose. By WILLIAM S. HOFFMAN, PH.D., M.D., and ITALO F. VOLINI, M.D.	513
Studies in the Oral Administration of Penicillin. II. Results of Treatment of Pneumococcal Lobar Pneumonia and Other Acute Infections With Several Oral Penicillin Preparations. By WILLIAM S. HOFFMAN, PH.D., M.D., and ITALO F. VOLINI, M.D.	520
The Serologic Response Following Penicillin Therapy for Early Syphilis. By E. GURNEY CLARK, M.D., R. W. MAXWELL, M.D., and VIRGIL SCOTT, M.D.	535
The Absorption and Elimination of Sulfadiazine Administered as Tablets, as a Ground (Micronized) Powder and as Microcrystals. By ELDON M. BOYD, M.A., M.D., C.M., and R. W. DINGWALL, M.D., C.M.	549
The Effect of Sodium and Potassium Lactates Upon the Absorption and Elimination of Microcrystalline Sulfadiazine. By ELDON M. BOYD, M.A., M.D., C.M., and R. W. DINGWALL, M.D., C.M.	557
Hypothermia and Elevated Serum Magnesium in a Patient With Facial Hemangioma Extending Into the Hypothalamus. By F. WILLIAM SUNDERMAN, M.D., PH.D., and MAJ. WEBB HAYMAKER, M.C., A.U.S.	562
Clinical Studies of the Pharmacologic Effects of Tetraethyl Ammonium Chloride in Hypertensive Persons Made in an Attempt to Select Patients Suitable for Lumbodorsal Sympathectomy and Ganglionectomy. By ROBERT BIRCHALL, M.D., R. D. TAYLOR, M.D., V. E. LOWENSTEIN, M.D., and IRVINE H. PAGE, M.D.	572
The Role of Trauma as a Possible Etiologic Factor in Regional Enteritis. The Effect of Non-penetrating Trauma on the Small Intestine of Dogs. By M. A. SPELLBERG, M.D., and ALTON OCHSNER, M.D.	579
Generalized Capillary and Arteriolar Platelet Thrombosis. By LT. (JG.) JOHN R. CARTER, (MC) USNR	585
Hypoprothrombinemic Action of Quinine Sulfate. By LEO A. PIRK, PH.D., and R. ENGELBERG, PH.D.	593
Electrocardiographic Observations in Chronic Cholecystitis Before and After Surgery. By E. RUTH BREITWIESER, M.D.	598
Monoplegia Following Carotid Sinus Pressure in the Aged. By FREDERIC D. ZEMAN, M.D., and SHEPPARD SIEGAL, M.D.	603
Treatment of Carriers of Endamoeba Histolytica and Other Protozoa With Carbarsone, Chiniofon and Vioform. By JOHN H. ARNETT, M.D.	608

No. 6—JUNE

Post-exertional Orthostatic Hypotension. By LUDWIG W. EICHNA, M.D., STEVEN M. HORVATH, PH.D. and WILLIAM B. BEAN, M.D.	641
The Tyrosinase Inhibiting Action of Serum From Normal and Cancerous Patients. By WILLIAM C. STADIE, M.D., MARTIN PERLMUTTER, M.D., and DAVID ROBINSON	655
The Treatment of Syphilis of the Central Nervous System With Penicillin. By ALBERT HEYMAN, M.D.	661
The Oral Administration of Penicillin in Dogs. By R. B. STEBBINS, B.S., M.S., T. J. MACEK, B.S., M.S., and P. J. DAUGHENBAUGH, M.D.	671
Streptomycin in the Treatment of Certain Gram-negative Bacillus Infections of the Central Nervous System. By TOM F. PAINE, M.D., RODERICK MURRAY, M.D., H. WILLIAM HARRIS, M.D., and MAXWELL FINLAND, M.D. With the technical assistance of CLARE WILCOX	676

The Significance of the Myeloid Maturation Curve in Material Aspirated From the Sternal Bone Marrow. By S. P. LUCIA, M.D., and MARJORIE L. HUNT, M.P.H.	686
Treatment of Pernicious Anemia With Synthetic L. Casei Factor. By NATHANIEL B. KURNICK, M.D. With the technical assistance of Miss GERTRUDE LURINSKY	694
Renal Filtration Rates in Pregnancy Toxemia. Inulin and Exogenous Creatinine. By LESTER D. ODELL, S.B., M.D.	709
Plasma Angiotonase Concentration in Normal and Toxemic Pregnancies. By ERNEST W. PAGE, M.D.	715
Diagnosis of Generalized Amyloidosis by the Congo Red Test: Definitive Diagnostic Criteria. By IRVING J. SELIKOFF, M.D.	719

NEW BOOKS AND NEW EDITIONS

Book Reviews and Notices	125, 250, 380, 511, 635, 756
New Books	127, 639, 759
New Editions	128, 640, 760

PROGRESS OF MEDICAL SCIENCE

MEDICINE	97
The Diagnosis of Pulmonary Disease. By L. L. FRIEDMAN, M.D.	
NEUROLOGY AND PSYCHIATRY	109, 115
Personality Repercussions of Anterior Poliomyelitis. A Review of the Literature. By CLYDE E. STANFIELD, M.D.	
Psychosomatic Relationships in Acute Anterior Poliomyelitis. By FRANKLIN G. EBAUGH, M.D., and CLARENCE S. HOEKSTRA, M.D.	
SURGERY	233
Plasma Substitutes. By C. EVERETT KOOP, M.D.	
OPHTHALMOLOGY	241
Exophthalmos of Endocrine Origin. By T. G. MARTENS, M.D.	
PREVENTIVE MEDICINE AND EPIDEMIOLOGY	362
Flea Versus Rat Control in Human Plague. By JOHN E. GORDON, M.D., and PHILLIP T. KNIES, M.D.	
DERMATOLOGY AND SYPHILOLOGY	494
Virus Pyogen and Virus Pyogen Photosensitivity Relationships in Cutaneous Disease. By JOHN H. STOKES, M.D., and HERMAN BEERMAN, M.D.	
OTO-RHINO-LARYNGOLOGY	502
A Survey of Current Trends. By NOAH D. FABRICANT, M.D.	

Therapeutics	611
The Present Status of Tryparsanide in Syphilotherapy. By HERBERT KOTEEN, M.D.	
Radiology	621, 628
The Medical Use of Radioactive Isotopes. I. Radioactive Isotopes in Hematologic Disturbances and Neoplasms. By BYRON E. HALL, M.D., and CHARLES H. WATKINS, M.D.	
The Medical Use of Radioactive Isotopes. II. Radio-iodine and the Thyroid. By F. RAYMOND KEATING, JR., M.D.	
Pediatrics	728
Sickle Cell Anemia. Recent Progress of Pediatric Interest. By BENJAMIN DICKSTEIN, M.D., and IRVING J. WOLMAN, M.D.	
Gynecology and Obstetrics	737
The Vagina. By FRANK B. BLOCK, M.D.	
Proceedings of the Physiological Society of Philadelphia	122, 246, 377, 509, 632, 754

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JANUARY, 1947

ORIGINAL ARTICLES

THE MIGRAINOUS PERSONALITY AND CONSTITUTION

THE ESSENTIAL FEATURES OF THE DISEASE: A STUDY OF 500 CASES.

By WALTER C. ALVAREZ, M.D.

ROCHESTER, MINNESOTA

(From the Division of Medicine, Mayo Clinic)

IN spite of all the research that has been done to explain the mechanism back of sick headaches,⁶ migraine is still one of the most poorly recognized, poorly understood, and poorly treated of all the common tormentors of mankind. Today, although we physicians know that the cause of the disease is a hereditary predisposition, that the "storm" arises in the brain, and that the digestive tract is upset only secondarily, we go on acting as if we still believed that we could find, somewhere in the patient's body, a localized cause for all the headaches. Perhaps in desperation or because the patient and her home physician expect it, whenever a woman with a perfectly typical story of migraine comes in, most of us internists promptly put her through the whole diagnostic mill again, even when she brings with her a sheaf of negative reports just given her by some able consultant.

Surely, this is not logical, and, surely, we ought to be able to do something more useful for the woman than this. If, as I shall show in this paper, the frequency with which attacks of migraine come, and their severity, depend largely on the woman's psychic makeup and on the amount of strain under which she lives, then we physicians should be spending most of the time we can give her in study-

ing her life problems and advising her about them. Furthermore, we should keep remembering that even if the tests and examinations we order were to reveal something locally wrong and this were to be corrected, the chances are great that the migraine would not be much improved. I learned this 35 years ago when, in my youthful enthusiasm, I promised a migrainous woman that if she would part with a gall-bladder full of stones she would be well. She had the operation, and the minute she got back home to face a family row, she had one of the worst sick headaches of her career. Since then I have seen hundreds of such women who had parted with appendix, gall-bladder, uterus, tonsils or teeth without getting help. Evidently the way to a cure rarely lies along that road.

Every physician who would treat migraine with some degree of success must realize and keep remembering that the trouble is an inherited nervous makeup "which is as definite a part of the economy of a person as the color of his eyes."² This predisposition is likely to remain for the duration of life no matter how many operations are performed or how many drugs are given. No one today with a good understanding of migraine would

ever hope to work a "cure" with any drug or regimen.

THE HEADACHE IS ONLY ONE OF THE MIGRAINOUS PERSON'S TROUBLES. Years ago, a woman helped me to get the proper understanding of the problems of the person with severe disabling migraine when she said, "Why do you keep talking about my headaches? I am not so concerned about them. I know how to avoid many of them, and I can stand the rest. What I want you to see is that even if I were to lose the headaches, I'd still be far from well. What I desire to be rid of is this tenseness and nervousness, and particularly this easy fatigability and sickness which have limited my activities ever since I was a girl. I want to be able to keep an engagement after I make it; I want to be able to keep up with my strenuous husband; I want to be able to go on a trip with him without having to cave in and rest up every few days, and I want to be able to stand a bit of excitement or worry or loss of sleep. I want to be rid of these awful days when I am depressed, detached from the world and half alive; to sum up, I want to be made over into a normal, strong human being."

Since that day I have come to see more and more clearly that the essential attribute of the typically migrainous person is his or her peculiar physical and mental and spiritual makeup. After studying hundreds of women with this disease, I am impressed with the fact that in most cases they are unusual persons, above the average in intelligence, with a distinctive personality, and often a distinctive appearance; sometimes so distinctive that one can suspect the nature of the trouble the minute the individual walks into the office. I keep saying "woman" because most of these patients are women. If, as Allen¹ claimed, the sons of migrainous parents inherit the tendency equally with the daughters, they must have an easier time with it because it seldom causes them to consult a physician.

THE NATURE OF THE MIGRAINOUS WOMAN. My impression is that the

migrainous woman tends to be somewhat short of stature, with a trim, well-proportioned body, better than average looks, and skill in dressing well. Her eyes are bright and expressive, her face is intelligent, and her responses and movements are quick.

The physician should learn to recognize these women because in the office so few of them think to mention the fact that they have or have had sick headaches, and some even conceal the fact; a few are so resentful of their handicap and the fact that it causes them to break engagements at the last minute that they will even deny its existence. Most of them, when giving their history, tend to ramble on about what this doctor said and that one prescribed until all the internist can conclude is that the trouble is probably some sort of a neurosis. It is well, therefore, if he can promptly recognize the migrainous facies and personality because then he can ask about sick headaches, and once the woman has admitted that she has them, he can quickly draw out the rest of the story. Then, because the migrainous tend so strongly to suffer in certain ways, the whole problem of diagnosis and treatment will be greatly clarified. In some cases in which there are no headaches at all he can draw out a story of so typical a temperament, so typical a family history, and perhaps so typical a cyclic vomiting in girlhood that he can be fairly certain about the migrainous nature of a hitherto puzzling abdominal distress—enough so as to save the woman from a futile exploratory laparotomy. In many a case he will quickly see that the woman's migrainous makeup can easily explain her life-long frailness and poor health, her tendencies to fatigue, faintness, dizziness, nausea, or gastric stasis, and her occasional days of depression.

Years ago, I was often unable to decide whether or not a certain headache was migrainous because I studied it as an isolated phenomenon. Perhaps I was puzzled because the pain was on both sides of the head or in the back of the

neck, or it was not preceded by a scotoma or followed by vomiting. Today, I often diagnose migraine with a fair degree of certainty just because the patient is a typically migrainous person who gets her queer spells in a typically migrainous way after becoming tired or tense or upset.

The following clinical picture is based on my observations made during a study of more than 500 patients with migraine, most of them women. To avoid bias, I waited until I was done to reread the outstanding papers of H. G. Wolff,^{10,11} and to go over other good studies of the migrainous personality by Moersch,⁵ Touraine and Draper,⁸ Knopf,⁴ Slight⁷ and Trowbridge, Cushman, Gray and Moore.⁹ I was then much impressed with the closeness of agreement of my observations with most of those made by the other investigators in this field. Strangely, women with migraine are often more like other women with migraine than they are like their own sisters.

THE OUTSTANDING CHARACTERISTICS. The outstanding characteristics of the migrainous woman are her hypersensitiveness, her quickness of thought and movement, and her tendency to get tense, to worry, to tire easily, to wilt suddenly and to sleep poorly. Usually, she is a perfectionist who works fast and accurately and likes to push other persons along to work fast with her. Anything out of the ordinary is likely to upset her. As one woman said, "When a child, I never got to a picnic because I always got sick from anticipation." Another said, "I never packed my bags to go on a trip; mother had to do it because I was too busy vomiting from excitement." Naturally, then, the migrainous woman is a poor traveler and sightseer; she must not shop too long, and she must avoid bustle, noises, bright lights and smells. In a restaurant she wants quiet, dim lights, and a table far removed from the orchestra and the kitchen door. She dislikes crowds, and hence she usually avoids functions. She is usually so sensitive to light that I suspect migraine the minute a woman

starts shading her eyes and blinking at my office window.

Easy Fatigability. Perhaps the greatest curse of the migrainous woman is her easy fatigability, which is probably in-born and due to her peculiar nervous system. This is shown by the fact that often it comes in girlhood before the headaches, and persists in later life after they have left. Characteristic of migrainous fatigue is the suddenness with which it overwhelms the victim: one minute she may be enjoying some shopping and the next she may be so exhausted that it is an effort for her to get to the street and into her car.

Much of the fatigue of these women is, of course, brought on by the distress which results from their abnormal sensitiveness and the intensity with which they react to happenings in the world about them. This acute and sympathetic responsiveness gives them much of their charm but it costs them dear. For instance, a usually calm and sensible migrainous woman, on answering the telephone, was told that a certain city was calling. Instantly fear struck at her heart because her daughter and grandchildren lived there. Surely, the child must be very ill. By the time the circuit was completed and she learned that it was a business call for her husband, she was so tense that she slipped on into a headache.

Naturally, when throughout the day many such stimuli keep beating in so intensely on her brain the woman must get tired. She gets tired from putting too much emotion and concern into little things. Her desire for perfection causes her to overwork. Her house must be spotlessly clean and run just so, and commonly she goes over again what has just been done by her maid. More fatigue is caused by her tendency to hurry, and to try to do several things at once, or by concern and tension over the work which she sees waiting to be done. Thus a woman bankteller with migraine always began to go to pieces nervously when the

line in front of her window got beyond a certain length.

More trouble arises because, with her high degree of intelligence, her tendency to think clearly, her faculties of leadership and her willingness to assume responsibility and to bear it conscientiously, the migrainous woman usually has dumped on her all the burdens and worries of her family group. She is the one to whom they all go with their problems and sorrows. In addition she often carries too big a load of leadership in clubs and civic and charitable organizations.

More fatigue comes because with her tenseness and her abnormal awareness of everything going on about her, the migrainous woman is often a poor sleeper who tosses about and wakes frequently during the night.

Tenseness. As already noted, a prominent characteristic of the migrainous woman is her tendency to get tense even from thinking of doing something. Sometimes she gets so tense from planning a dinner party that by the time the guests arrive, she is in no condition to greet them, let alone to sit down to eat with them. This story is so typical that the minute I hear it, I have little doubt about the diagnosis of migraine. Because of the great tenseness of the nuchal muscles, many a woman's sick headaches start at the back of the neck. If these persons could only learn to work and think without getting tense many would be well. Curiously, some of them get their attack when a strain lets up, as at Saturday noon time and then they may speak of a "let-down headache."

Twilight Spells (Dämmerzustände, Dysphrenia Hemieranica Transitoria). The typically migrainous woman has days in which she is a bit depressed, apathetic, dazed or confused, uncommunicative, disconnected from the world about her, and utterly miserable, much as if she were in a migrainous attack without the headache of the nausea. In such spells she usually has little desire for food, or ability to eat it. She may be able to do some

work but she pays little attention to those about her. To illustrate, 1 day when in such a spell, a young woman met her favorite uncle on the street. Nodding casually, she walked on. Astounded and puzzled, the uncle followed and asked for an explanation. All she could say was that, dazed and miserable, she had been in no mood to stop and talk. On another day she, usually a delightful hostess, treated a week-end guest so diffidently that he felt he must in some way have offended and that he had better pack and go. Fortunately, shortly after noon she began to come out of the haze in which she had been living, and soon she was her merry and charming self again.

An Element of Masculinity. Although in most ways the migrainous woman is decidedly feminine and sexually attractive, she often has a masculine element in her nature which causes her to act independently and to think dispassionately much as does an able businessman. She has little patience with the small talk of the average uneducated woman, and prefers to chat with well-informed men about the important problems of life.

MARITAL PROBLEMS OF THE WOMAN WITH SEVERE MIGRAINE. According to some writers, many women with migraine fail to make a good marital adjustment; they either do not love deeply or they love more with the brain than with the heart and body. My impression from the histories given me is that most migrainous women are normal sexually and that when they are unhappy in marriage, it is usually because they are not in love with their mate. The migrainous woman is often dissatisfied with what by most of her sisters would be considered a good husband, and this is due to her great desire for perfection and for a life lived richly, beautifully, eventfully and romantically. The fact that the mate is a good provider, steady, kind, and devoted is not enough to bring her contentment.

Because of her peculiar temperament and frequent illnesses, and hence her great need for kindly, sympathetic and

understanding care and consideration, the migrainous woman who is more than usually frail and sickly must find an angel and a good provider for a husband, and it is remarkable how often she succeeds in doing just this. Naturally, when she marries too early, before she knows what a kind, devoted, self-sacrificing and undemanding type of companion and male nurse she will need, she sometimes makes a bad choice; she picks a glamorous scallawag, and then she must either get a divorce or spend the rest of her days unhappily. In such case the woman's mental distress and her inability to decide what to do about the marriage commonly account for the frequency with which the headaches keep coming.

But even when she gets her "angel" she is sometimes unhappy because, in order to secure the essential attributes of kindness, indulgence and financial stability, she may have had to give up other attributes which she had long dreamed of in her Prince Charming, attributes such as physical and sexual attractiveness, colorfulness, masterfulness and lover-like ways. Not infrequently, the man she gets is inarticulate and without skill in the ways of making a woman happy. In some cases he depends on her too much for decisions and encouragement; in others she finds he is beneath her in intelligence or ability, and that bothers her. At any rate, he never succeeds in winning her, and in secret she keeps grieving and wishing that she could be unkind enough to leave him.

The husband is usually satisfied with his bargain because his wife, when well, is such an interesting and delightful companion that he is willing to put up with the inconvenience and expense of her many illnesses. As he says, he would rather have what little he gets from an unusually attractive woman than much more from an ordinary woman of no distinction.

.. MIGRAINOUS TEMPERAMENT IN MEN. Study of a number of migrainous men has shown me that they, too, tend to have the

temperamental characteristics noted in the women. Most remarkable as an apparent exception that "proved the rule" was the case of a stocky uninteresting-looking farmer who complained of many symptoms. I could hardly believe my ears when he told me he suffered from sick headaches, with a scintillating scotoma and nausea and vomiting. He did not look the type, but soon I found that, except for the lack of high intelligence and social charm, he was typically migrainous. He had always been nervous, overly irritable, and prone to fatigue quickly. After half a day's work he had to go to bed. He slept poorly; he was often tense and jittery, and then sometimes he suffered from curious abdominal pains. He was typically hypersensitive to light and sounds, and his subcutaneous tissues everywhere were abnormally sensitive. He could not read much because his eyes tired so quickly, and he was too nervous to talk long to anyone or to go into a crowd. He had the typical desire to get his work done quickly and well, and he had the "half-alive days."

THE HANDICAP OF AN ADDITIONAL INHERITANCE OF ALLERGY, HYPERTENSION, DYSMENORRHEA OR PSYCHOPATHIC DISORDERS. Much of the literature on migraine is confusing because the writers did not see that the severity of the disease and the clinical picture it presents in an individual is often modified by the addition of a second harmful inheritance. Thus some allergists, on finding sick headaches afflicting many of their patients, jumped to the conclusion that migraine is simply a manifestation of allergy, while others, on finding sick headaches, more than usually frequent among persons with hypertension, might well have assumed that migraine is a manifestation of high blood pressure. Actually, I always think of the migrainous storm in the brain as being like a mousetrap set off by a trigger. Allergy is just one of the things that can spring the trap, and hypertension is one of the things that can set the trigger

so finely that the trap can almost go off by itself.

Mild Forms of Migraine Can Be Intensified. During recent years, by asking all my bright-looking women patients if they have ever had sick headaches, I have learned that there are many who have had migraine in a form so mild or they have had the attacks at such rare intervals that they do not think to mention them. Others, as Buchanan pointed out, doubtless carry latent a tendency to the disease. They resemble those many typically epileptic persons who never have had a fit. Other migrainous persons have enough bad genes to get the temperament and to have brilliant scintillating scotomas but never the headache or the nausea. Now, just let a woman with such a slight tendency to migraine get some extra handicap or sensitizer such as rising blood pressure, or great psychic strain, and soon severe headaches may be upon her.

It is true that a high percentage of migrainous persons are markedly allergic, but I think their sensitivity to dust, pollen and foods is part of their exaggerated sensitivity to all stimuli. That migraine is not just a manifestation of allergy should be obvious to anyone who has watched many of the victims continuing to have sick headaches long after they have identified all offending foods and eliminated them from the diet. Evidently these foods constituted only some of the triggers that could start an attack, and after they were gone plenty were left such as fatigue, excitement, worry and tension. A common one is menstruation, especially when it is accompanied by the somewhat psychopathic tension that occasionally ushers in the period in the case of severe migraine. Less common as a trigger is constipation, and probably still less common is eyestrain or imbalance of ocular muscles.

As one would expect, many of the persons with the severest forms of migraine owe their desperate situation to the workings of an added psychopathic inheritance. This has caused them to wear themselves

down with inner conflicts, unhappiness, frustration, needless worries and difficulties in adjusting to life and to contacts with persons round about them. Often the woman gets herself into a miserable state fretting over silly scruples, fighting compulsions or spending half the night trying to make a simple decision. Perhaps because of a somewhat dual personality, she will get worn out with the struggles between her fine, gracious, kindly and idealistic self and perhaps a spoiled, bitter-tongued, self-centered, short-tempered, vindictive or steely-hard self.

Whenever I see a woman who is having more than 3 bad headaches a week, I am almost certain that either she fits into this psychopathic group or else, somehow, she is misusing her brain. Either she is carrying burdens of work or responsibility much too heavy for her, or she is struggling with a life problem she cannot solve, or she does not get enough rest, or all through the night she keeps thinking in squirrel-cage-fashion; or to paraphrase Omar, she evermore comes out by the same door as in she went.

In the case of many a woman, migraine is extra severe and disabling because she inherited a frail and sickly body, too weak to stand up properly to the strains of life. Often she has defective and poorly functioning pelvic organs, and the dysmenorrhea, severe monthly storms, and perhaps fatigue resulting from a series of operations are likely to add to her susceptibility to headache. As everyone knows, in many cases the alternate cycles of secretion in the pituitary body and the ovary have much to do with determining when the headaches come, perhaps because they set the trigger more finely.

In these many cases with several bad inheritances it is only a wise old clinician who can hope to unscramble the complicated story into its several components.

THE MIGRAINOUS TEMPERAMENT AND THE TREATMENT OF THE DISEASE. A knowledge of the migrainous woman's temperament and usual life problems helps tremendously when it comes to the matter

of treatment. Knowing what her besetting sins and sources of distress usually are, the physician is likely within $\frac{1}{2}$ hour to get to the heart of her problem. As I have pointed out, often there is a secret story of unhappiness or strain, and only by getting the patient to confide it to him can the physician hope to help her. Often he can help by assisting her to decide finally what she is going to do about a difficult situation in home or office. He will help also by teaching her to rest her brain, to avoid tenseness, and to get mental peace and enough sleep. Often if she can only get a good long rest in the country or in the home of a loved relative, the trigger will get 'set so firmly that for months nothing can trip it.

Theoretically, bromides, phenobarbital, or dilantin (diphenylhydantoin sodium) should help; but curiously, in bad cases in which there has been great need for something to quiet the brain and thus lengthen the interval between attacks, I have found these drugs ineffective. Many of the patients I see have been treated with endocrine products without avail.

Oftentimes almost a cure is worked when a woman's fear of her attacks is cleared away, when she knows what her disease is, and that she has not a brain tumor or any organic disease in the abdomen, and that to a large extent she can determine the number of spells she is to have. Later, as she sees that most of her headaches follow periods of overwork or strain or fretting or worrying, she may so mend her ways as to be almost well.

In this article I shall not go into a discussion of the treatment of the headaches as I have done that elsewhere.³

Summary. Since migraine is an entity, a hereditary disease of the brain, it is not logical to keep searching through the patient's body for the basic cause of the trouble. Even when organic disease is found in the digestive tract and removed, the headaches may go on unchanged or they return after a while.

The nausea and vomiting of migraine are due to reverse peristalsis instituted by

a storm that comes down from the brain, perhaps along the vague nerves, as in seasickness. Since the tendency to migraine is built into the patient's nervous system, no one can hope to eradicate it with any treatment.

The headache is only one of the migrainous person's many troubles. Often more distressing are a general sickliness, nervousness and easy fatigability. The migrainous person often has a peculiar and recognizable mental and spiritual makeup. Usually a woman, the patient often has a trim, well-proportioned body; her eyes are bright and expressive, and her face is more than usually intelligent.

The physician should learn to recognize these women because in the office so few mention their sick headaches. Given the information that the headaches occur, the diagnosis often becomes easy because the migrainous person tends so strongly to suffer in certain known ways.

In the absence of headaches, but with a typical migrainous temperament, a typical family history, and, perhaps, typical cyclic vomiting in childhood, the physician can say that an abdominal distress, or vomiting, or a dizzy spell is probably a migrainous equivalent. Or he can diagnose migraine simply because the patient is typically migrainous and gets her spells in a typically migrainous way after becoming tired or tense or upset.

Migrainous women are generally hypersensitive to light, sounds and smells; they are quick of thought and movement; they tend to get tense, to worry, to tire easily, to wilt suddenly and to sleep poorly. They are perfectionists. Anything out of the ordinary upsets them. They often carry too much responsibility with too great conscientiousness. They put too much emotion into little things. They get tense just from thinking of work that is to be done, and this often brings a headache.

Many migrainous women have days when they are a bit depressed and detached from the world, and hazy in their

thinking. Many are somewhat dissatisfied with their marriage.

In many persons migraine is a mild disease, or it may even be carried latent; in others, the tendency is converted into a disabling disease by an additional inheritance of allergy, hypertension, dysmenorrhea, psychopathy, or constitutional inadequacy.

Any woman having more than 3 migrainous headaches a week is usually either psychopathic or is misusing her brain in some way, or her burdens are too heavy for her.

In many cases that might otherwise be very puzzling, a knowledge of the migrainous temperament helps greatly in diagnosis and treatment.

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FATAL INFECTION WITH POLIOMYELITIS VIRUS IN A LABORATORY TECHNICIAN

ISOLATION OF VIRUS FROM LYMPH NODES*

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It is our purpose in this report to describe a fatal case of poliomyelitis which occurred in a technician, 26 years of age, who had been exposed in his work to strains of poliomyelitis virus. The circumstances are such as to make it probable that his infection was contracted in the laboratory. To our knowledge this is the second instance in which accidental infection of this type has been reported, the first instance being recorded by Sabin and Ward in 1941.¹⁷ Their case, which was non-fatal, occurred in a woman of 35 who had been preparing virus suspension from the tissue of cynomolgus monkeys infected with strains recently isolated from human sources. Sabin and Ward have emphasized the dangers to humans of exposure in the laboratory to tissues or excreta of human beings with poliomyelitis. They also emphasized the dangers of working with the highly susceptible cynomolgus monkeys when infected with such strains. For this reason, we also have been concerned in this report with the circumstances in our own case under which sickness occurred. We have considered the central nervous system lesions carefully and have carried out virus isolation studies, both of these being directed in the hope of detecting the portal of entry in this case.

Case Report. W. G. D., a mechanical engineer, 26 years of age, was admitted to the New Haven Hospital on Aug. 24, 1945.

Past History. He had been quite healthy all his life. Tonsillectomy had been performed at the age of 7. In 1943 he had had

bacillary dysentery. Early in 1945 he was admitted to the New Haven Hospital suffering from slight fever and upper abdominal pain. No satisfactory diagnosis was reached at that time.

Occupational History. He had received university and practical training prior to 1943, in laboratories designed for research in engineering. In October 1944, he applied for and was accepted as a technician in the Yale Poliomyelitis Study Unit. He proved to be a careful worker and was trained during 1944-1945 to assist in certain technical procedures. These involved the preparation of virus suspensions and centrifugation prior to their inoculation into experimental animals. During the first 6 months of his apprenticeship he worked under close supervision. During his entire period of employment he worked under guidance.

The infective materials used by this technician were of human and simian origin and included feces, pharyngeal washings and central nervous system tissue. In preparing inocula he ground the material with mortar and pestle; resulting suspensions were then homogenized in a Waring blender, and centrifuged in various types of high speed centrifuges. During the 2 months preceding his illness, work with human material and "human" strains was being carried out in the laboratory, but not more extensively than in the previous 8 month period. In July and August 1945 he assisted a staff member in feeding poliomyelitis virus (recent human strains) by stomach tube to infant rhesus monkeys.⁴

During July and August 1945, W. G. D. did not leave the city of New Haven on any visits to outside places. Within this period and afterwards, relatively few (19) cases of poliomyelitis occurred in the area where he

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Skin. The scratch mark on the dorsum of the right wrist was present.

Lymph Nodes. Two nodes obtained from the left axilla were larger (2 to 3 \times) than those on the right, which were of normal size. Lymph nodes from neither side revealed gross evidence of acute infection. Other lymph nodes, including the mesenteric lymph nodes, were grossly normal in appearance. When studied histologically, none of these nodes showed definite alterations from the normal picture and a search for atypical cells (Giemsa's, hematoxylin and eosin, and reticulum stains) was negative in half a node (which did not contain virus; see Monkey 30-76, Table 1) from the right axilla.

Thoracic Viscera. The lower lobes of the lung were firm, non-crepitant, and pink frothy fluid oozed from the cut surface. Histologic sections revealed focal bronchopneumonia, pulmonary edema and hemorrhage. A focal interstitial myocarditis demonstrable histologically was present also.*

Brain and Cord. The pia mater was cloudy, particularly in sulci over the temporal and occipital lobes of the brain. The base of the brain appeared normal except for a cerebellar pressure cone. Histologically, lesions of poliomyelitis were widespread. Lesions were also found in the olfactory bulbs. Severe damage occurred in the mid-brain, pons, medulla and in the spinal cord.

In a single preliminary section taken longitudinally through the olfactory bulbs no lesions were seen. When serial sections (about every 10th section was stained) were examined some of the blood-vessels in the anterior olfactory nucleus were heavily cuffed with lymphocytes (Fig. 2). These perivascular lesions were deep seated in the olfactory bulbs. Very few, and scattered lesions with questionable neuronophagia were present in the peripheral mitral cell layer.† Otherwise there was no evidence of neuronophagia or inflammatory glial response. Lesions were present in 1 olfactory bulb, the other being entirely free.

Diagnosis: Acute bulbar poliomyelitis, bronchopneumonia, acute myocarditis.

Subsidiary: Old pancreatitis; atrophy of left testicle.

* Similar changes were found in the myocardium of another case recorded in this paper (D. D.). Such lesions have received attention in the literature on the pathology of human poliomyelitis and have been referred to by Saphir and Wile,¹⁹ among others.

† Dr. Howard A. Howe and Dr. David Bodian of the Poliomyelitis Research Center, School of Hygiene and Public Health, Johns Hopkins University, Baltimore, Md., very kindly examined the histologic material from the brain and cord of this patient. We have made free use of their descriptive comments in summarizing the findings in the olfactory bulbs.

Histologic changes like those which we observed in the anterior olfactory nucleus and mitral cell layer have been observed previously,²⁰ but their occurrence in human cases⁵ is distinctly unusual. Although it may not be clear in this case whether the lesions in the olfactory bulb indicate ingress or rostral spread of virus we are inclined to believe that the lesions represent an extension forward from the brain. The evidence for this is based in part on the absence of lesions in the periphery of the olfactory bulb.

ISOLATION OF VIRUS FROM THIS CASE (W. G. D.) Various types of material were obtained for virus studies from this case. These included:

(a) *Antemortem material* consisting of pharyngeal secretions, and material from a cotton swab which had been rubbed on the surface of the oropharynx. Both specimens were obtained on August 24, the 7th day of his disease and 2 days prior to his death.

(b) *Autopsy material* consisting of: central nervous system tissue, lymph glands, blood, portions of the spleen and washed wall of the upper and lower intestine, and the colon contents.

The procedures for the removal of tissues for virus studies of this type are important and for this reason are mentioned in detail. Essentially we have followed the technique of Sabin and Ward.¹³

Technique of Removing Tissue. Sterile instruments were used for each different tissue. Following incision across the chest, right and left axillary nodes were removed and placed in separate lusteroid tubes, for freezing. The abdomen was then opened. Here a break in technique occurred for the stomach wall was accidentally punctured and about 20 cc. of its contents escaped into the peritoneal cavity. Mesenteric lymph nodes were removed, then

the spleen and lastly the gastro-intestinal tract, which was placed on sterile wrapping paper. A central core of spleen was removed for virus study. Segments of duodenum, ileum and descending colon

were tied, cut, and each placed in separate cardboard boxes, and then on dry ice.

The calvarium and the vertebral laminae were carefully removed without sterile precautions, with the dura mater intact. The

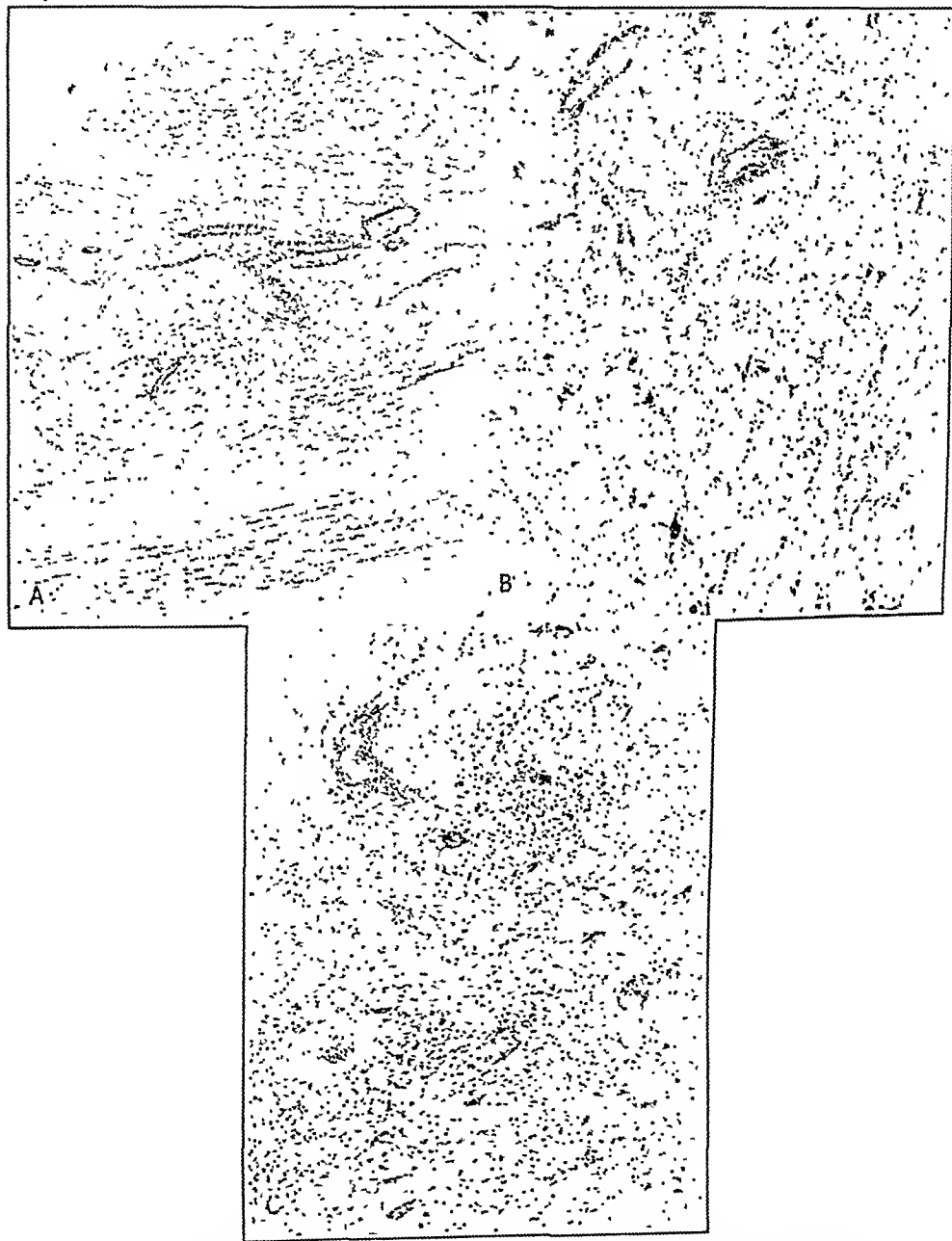


FIG. 2.—Histologic lesions seen in several segments of W. G. D.'s central nervous system. *A*, Anterior olfactory nucleus ($\times 35$). *B*, Midbrain ($\times 70$). *C*, Cervical cord ($\times 70$).

dura was opened with sterile instruments, and the brain placed on a piece of sterile wrapping paper and segments of cord and brain stem were later removed for virus study.

All material was kept frozen on dry ice until tested. These tests were begun 1 month after the material was collected and they were completed within 3 months.

Preparation of Material for Inoculation. Oropharyngeal swabs were eluted by a method described by one of us (H. A. W.) in a previous note.²⁵ 1 cc. of the eluate was given intracerebrally and 2 cc. intranasally to Monkey 31-55. To 4 cc. of pharyngeal secretion 1 cc. of phosphate buffer at pH 4 was added; 1 cc. of this material (pH 5.5) was given intracerebrally and 4 cc. intranasally to Monkey 31-56.

Colon Content. Extracts were prepared for inoculation using various methods.^{13,21} Generally 10 cc. was given once intraperitoneally and 5 cc. twice intranasally to Monkeys 31-54 and 31-64. Occasionally 1 cc. of the ultracentrifuged inoculum was given intracerebrally cf. Monkeys 31-42 and 31-43. (Table 2.)

The following tissues collected at autopsy were triturated individually to make a 10% suspension by weight in sterile distilled water, *viz.*, central nervous system tissue; right and left axillary nodes. These suspensions were spun at 2000 r.p.m. for 10 minutes and 1 cc. of the supernate was inoculated intracerebrally into monkeys. The mesenteric nodes and splenic tissue were rinsed in 5 changes of sterile distilled water, prior to trituration. The intestinal segments, namely duodenum, ileum and descending colon were opened (each done on a different day) and their contents, excepting that from the lower colon, discarded. Using sterile gloves the serosal and mucosal surfaces of the intestinal segment were washed by gentle rubbing with the finger and rinsed in 7 changes of distilled water. The washed tissues were triturated and suspensions prepared which were centrifuged as above, and 1 cc.

inoculated intracerebrally into a monkey. Culture of the duodenal emulsion (0.05 cc.) yielded 8 colonies of *B. coli* on a blood agar plate. The emulsion of ileum proved sterile to culture; 24 colonies of *B. coli* were counted on the blood agar plate seeded with 0.05 cc. of extract of descending colon. "Whole blood" was prepared by breaking up the clot; 1 cc. of blood was inoculated intracerebrally and 5 cc. intraperitoneally into a monkey.

Animals Inoculated. Seven rhesus (*Macaca mulatta*) and 13 vervet (*Cercopithecus æthiops centralis*)¹⁵ monkeys weighing between 1.5 and 3.5 kg. were used for these tests and were inoculated under full ether anesthesia. Unless the animal was killed earlier, monkeys inoculated intracerebrally were exercised daily and daily rectal temperatures were recorded for 4 weeks. Four monkeys were re-inoculated after 4 weeks of uneventful clinical observation (see Table 1). All animals which showed symptoms of poliomyelitis were sacrificed at what appeared to be an appropriate time. All other monkeys were sacrificed at the end of the 4 or 5 week experimental period.

Criteria for Identification of Poliomyelitis Virus. The criteria adopted for the identification of poliomyelitis virus in this laboratory have been outlined elsewhere.²³ Essentially they consist of the production in the monkey of an illness compatible with experimental poliomyelitis. Passage of the virus to a second monkey was attempted and accomplished in 1 instance with this strain (W. G. D.). This strain produced no evident disease in cotton rats, Swiss mice, or young adult rabbits.

RESULTS. A summary of the test performed on material from this case (W. G. D.) appears in Table 1. Virus was detected in the pharyngeal material; in the central nervous system (pons, medulla and cord); right axillary nodes (1 out of 2 trials); mesenteric lymph nodes; and duodenum (washed wall). Virus was not detected in the left axillary lymph nodes (4 trials—negative), blood, spleen, ileum (washed wall) and colon (washed wall).

The test with the colon contents was not completely satisfactory but may be regarded as negative.

VIRUS IN LYMPH NODES IN HUMAN POLIOMYELITIS. For comparison we have therefore analyzed previous work on the isolation of poliomyelitis virus from human lymph nodes and have also included in this report (see Table 4) 2 other fatal cases of poliomyelitis which we have had occasion to study in this laboratory and from which lymph nodes obtained at autopsy, were tested for virus.

physician found his temperature to be 102° F. (oral). During the afternoon he was nauseated but did not vomit. By the next day (August 31) his left shoulder and right arm were weak. There were twitchings of his face and he had difficulty in speaking. He became drowsy and his respiration became labored and uneven.

He was admitted to the New Haven Hospital on September 1 (No. B-360). On admission his condition was critical. His respirations were irregular; breathing was difficult. There was moderate stiffness of the neck. The left pupil was smaller than the right.

TABLE 1.—TESTS FOR POLIOMYELITIS VIRUS IN TISSUES AND SECRETIONS FROM PATIENT W. G. D

Tissue or secretion	Date of collection	Dosage and portal	Monkey inoculation		
			Species and No.	Date	Results
CNS (medulla, pons, sp. cord)	8/26/45	1 ml. ic	R-3120	10/24/45	+
Pharyngeal secretion . . .	8/24	1 " "	R-3156	11/15	+
		4 " in			
Pharyngeal swab	"	1 " ic	R-3155	11/15	+
		2 " in			
Lymph nodes:	8/26				
Rt. axillary (pool)	"	1 " ic	V-3031	9/29	+
Rt. axillary (½ node)	"	1 " "	V-3076	10/17	—
Left axillary (pool)	"	1 " "	V-3074	10/15	—
		1 " "	V-3074†	11/13	—
		1 " "	V-3075†	11/13	—
		1 " "	V-3077†	11/14	—
		1 " "	V-3034	10/15	+
Mesenteric	"	1 " "	V-3077	10/17	—
Blood	"	1 " "	V-3077	10/17	—
		5 " ip			
Spleen	"	1 " ic	V-3075	10/15	—
Duodenum (washed wall)	"	1 " "	V-3078	10/18	+
Ileum (washed wall)	"	1 " "	V-3079	10/18	—
		1 " "	V-3076†	10/14	—
Desc. colon (washed wall)	"	1 " "	V-3080	11/9	—
Colon contents	"	10 " ip	R-3154	11/10	..
		10 " in	R-3164	11/21	—
		1 " ic*	R-3142	12/14	..
		1 " ic*	R-3143	12/16	..

ic = intracerebral, in = intranasal, ip = intraperitoneal route of inoculation; * = ultracentrifuged material; R = rhesus, V = vervet monkeys; † = monkey used a second time in this experiment; + = experimental poliomyelitis, — = negative, .. = incomplete test.

These case reports are as follows:

R. F., 30 years old, male telephone lineman, was well until Aug. 29, 1939, when he developed a stiff neck. The next morning (August 30) the muscles of the shoulder girdle felt sore and stiff. Within a few hours he noted numbness and some weakness in his left hand, and complained of headache. A

Biceps and triceps reflexes were absent on both sides.

His *clinical course* progressed swiftly downhill. He was placed in a respirator. Shortly after admission he lapsed into a comatose state. He died on September 2, the 5th day of illness.

A *postmortem* examination was begun 3 hours after death.

Autopsy Findings. The skin was intact. Lymph nodes were normal in appearance. The posterior segment of the lower lobe, left lung, was firm, reddish brown in color and non-crepitant. The spleen was enlarged; its pulp soft. The serosal surface of the cecum was stippled with petechial hemorrhages. On the cut surface of the brain, flame shaped hemorrhages were seen in the subcortical area. Small red dots suggestive of hemorrhage were also seen on the cut surface of the cervical cord.

Histologically, typical lesions of poliomyelitis were present in the spinal cord, medulla and pons. There was also extensive involvement in the region of the hypothalamic nuclei, and around the third ventricle. The olfactory bulbs (one section from each bulb) showed no evidence of inflammation. The histology of an inguinal lymph node appeared normal.

Diagnosis: *Acute bulbar poliomyelitis. Bronchopneumonia.*

D. D., 13 year old male, of Italian parentage became ill on Nov. 25, 1945, with chilly sensations and headache. On the day following he stayed in bed because he "felt weak." On November 27 he had sore throat, headache and chills. On awakening on November 28 he had pain in the upper part of his right arm. He choked when drinking water. His speech was thick. His right arm was weak and his neck hurt when he moved it. His temperature in the afternoon was 104° F. (rectal). He was admitted to the hospital on that day, November 28 (B-74723).*

His tonsils had been removed at the age of 3 years. He was large for his age and overweight but on the whole had been healthy.

On admission he was acutely ill. He was oriented, restless and apprehensive. He was unable to swallow a frothy brown colored sputum. His speech was thick. His neck was stiff. The gag reflex was sluggish, and

TABLE 2.—TESTS FOR POLIOMYELITIS VIRUS IN TISSUES FROM PATIENT R. F.

Tissue	Date of collection	Dosage and portal	Monkey inoculation		
			Species and No.	Date	Results
CNS (cervical cord)	9/2/39	1 ml. ic	R-1321	9/12/39	+
CNS (lumbar cord)	"	1 " "	R-1327	"	—
Lymph nodes:					
Cervical	"	1 " "	R-1322	"	—
Axillary	"	1 " "	R-1326	"	—
Inguinal	"	1 " "	R-1324	"	—
Mesenteric	"	1 " "	R-1323	"	—
Mediastinal	"	1 " "	R-1325	"	—

Legends as in Table 1.

Seven samples of tissue were removed at autopsy into sterile separate containers as aseptically as possible: cervical and lumbar cord; cervical, axillary, mediastinal, mesenteric and inguinal lymph nodes. Suspensions of these tissues were tested for poliomyelitis virus in 7 rhesus monkeys, all of which were inoculated intracerebrally. Virus was isolated from only 1 sample, namely, from the cervical region of the spinal cord. All the lymph nodes yielded negative tests. Results appear in Table 2.

the left side of the soft palate drooped. The right arm was weak; the right biceps reflex was absent. The ninth, tenth and eleventh cranial nerves were involved. A lumbar puncture revealed 40 lymphocytes per c.mm. of spinal fluid.

His *clinical course* in the hospital was brief. On November 29 he was restless, became disoriented and soon went into shock. He died on November 30, the 6th day of illness.

A *postmortem* examination was begun 3 hours after death.

Autopsy Findings. The skin was intact. Lymph nodes were normal in appearance.

* We are indebted to the Department of Pediatrics, Yale University School of Medicine, for the privilege of transcribing data from this patient's record, and to Dr. Charles Kennedy, of the Department of Pathology, for the opportunity of studying the autopsy material.

Subendocardial hemorrhages were visible on the wall of the left ventricle, the largest occurring on the interventricular septum. Fibrous adhesions covered the entire surface of the left lung. There were subpleural hemorrhages beneath the visceral pleura in the left apical and posterior segment. The brain and cord were not remarkable in their gross appearance.

case of W. G. D. The results of tests for the presence of poliomyelitis virus in lymph nodes and other tissues from this case appear in Table 3.

DISTRIBUTION OF VIRUS IN HUMAN LYMPH NODES. The findings in the case of W. G. D. fit somewhat irregularly into the pattern of previous workers on the

TABLE 3.—TESTS FOR POLIOMYELITIS VIRUS IN TISSUES FROM D. D.

Tissue	Date of collection	Dosage and portal	Monkey inoculation		
			Species and No	Date	Results
*CNS (medulla, pons, sp cord)	11/30/45	1 ml. ic	R-3176	12/6/45	+
Lymph nodes					
Rt axillary	"	1 "	V-3082	12/4	—
Left axillary	"	1 "	V-3083	"	—
Rt. inguinal	"	1 "	V-3085	"	—
Mesenteric (pool)	"	1 "	V-3084	"	—
		1 "	V-3086	12/10	—
Duodenum (washed well)	"	1 "	R-3178	12/6	+
Heart muscle	"	1 "	R-3177	12/5	—

Legends as in Table 1

TABLE 4.—TESTS FOR POLIOMYELITIS VIRUS IN LYMPH NODES OTHER THAN TONSILS RECORDED IN FATAL HUMAN CASES

Authority	Cervical	Axillary	Inguinal	Medastinal	Mesenteric
Flexner and Lewis (1910) ⁴	.				(1/1)†
Levaditi, Schmutz and Willemin (1931) ¹²	..		0/1		
Flexner (1936) ¹					0/8
Kling, Olin and Gard (1938) ⁹	1/2				4/33
Kempf and Soule (1940) ⁷					0/3
Sabin and Ward (1941) ¹³	0/7	(1/7)*	(1/7)*	.	0/6
Kessel, Moore, Stumpert, Fisk (1941) ⁸	.			.	0/14
R. F., New Haven Hosp. (1939)	0/1	0/1	0/1	0/1	0/1
W. G. D. + D. D., New Haven Hosp (1945)	.	1/2	0/1		1/2
Total	1/10	(2/10)†	(1/10)†	0/1	5/67

1/1 = 1 test positive in a sample from 1 patient.

* Axillary and inguinal nodes pooled.

† One positive test was from a pooled sample.

‡ More than 25 years later (1936) Flexner¹ pointed out that sterile technique had not been used in this determination and so the positive result could not be accepted as definite. This test has not been included in the total.

Histologically, typical lesions of poliomyelitis were present in the spinal cord, medulla and pons. There was moderate and extensive involvement in the posterior segment of the pons in the regions of the floor of the fourth ventricle and the aqueduct of Sylvius. The olfactory bulbs showed no evidence of inflammation.

Lymph glands were removed with the same precautions as those followed in the

distribution of virus in tissues and secreta from fatal human cases.^{6 9 16 18} There is one positive test which stands out rather prominently, namely the finding of virus in lymph nodes from the right axilla.

Various efforts to isolate poliomyelitis virus from extraneural human tissue obtained at autopsy have been made and reported from the time poliomyelitis virus

was first discovered. It will not be our plan to review these studies here but we will list the reports of all tests that have been made on lymph nodes other than tonsils. The history of this subject was mentioned in 1941 by Sabin and Ward.¹⁸ Although it goes back to 1910,³ most of the lymph nodes studies have been made within the last decade (see Table 4); they include the observations of Kling and his co-workers⁹ in Sweden; of Sabin and Ward,¹⁸ of Kessel *et al.*,⁸ and others (see Table 4). By far the greatest number of positive results have been obtained from the tonsils and attached pharyngeal mucosa,^{3,8,10,18} but the difficulties of obtaining such material free of contamination are such that we have made no serious attempt to evaluate the literature on this score.

To the tests recorded from the literature and listed in Table 4 we have added 3 other cases studied in our own laboratory, described herein and hitherto unpublished.

Discussion. Circumstances were such in the case of W. G. D. reported above to make it highly probable that his infection with poliomyelitis virus was acquired in the laboratory. It should be pointed out in this connection that this technician was exposed in his work to strains of poliomyelitis virus recently isolated from human cases. This was also the situation in the only other reported case of laboratory infection with poliomyelitis virus.¹⁷ According to a liberal estimate made from personal communications, and from published reports, it is our belief that during the decade 1936-45 not more than 50 to 75 people may have been actively engaged in laboratory work on experimental poliomyelitis in this country and Canada, *in which strains recently isolated from human sources were being used.* Considering the age of the average technical worker in the field, the theoretical attack rate of 2 per 50 to 75 adults is high.

It appears to us that manual work

with poliomyelitis virus is more dangerous as far as contagion or infection is concerned than is work with patients ill with poliomyelitis. It is therefore our purpose in this paper to emphasize again the really great dangers of exposing technical workers to strains of poliomyelitis virus of this type.*

Another purpose of this report is to consider the route through which this man might have been infected. Unfortunately this requires speculation but among other routes we must include the possibility of the cutaneous route. At least, we must recognize that poliomyelitis has been acquired accidentally in man by injecting the virus under the skin. These accidents (supposedly 10 in number) occurred when vaccination was being tried in this country in 1935.¹¹ It is known that monkeys can be infected by the cutaneous route^{21,22} and probably this applies to chimpanzees.¹⁴ It is conceivable therefore that the presence at autopsy in the case of W. G. D. of virus in the right axillary lymph node, as opposed to the left, might be a significant finding in view of the presence of a deep scratch sustained by this man on the right wrist during a period preceding his illness when he was working with strains of the virus. But, we do not feel at all prompted to promote the idea that infection was necessarily acquired through the skin in this particular case. We also do not believe that infection was necessarily acquired through the olfactory route, because of the location of lesions. In brief, therefore, the data presented have certain informative value, but they are not complete enough to allow one to say how this man acquired his infection.

Summary. 1. A fatal case of poliomyelitis is described which occurred in a laboratory worker. It is probable, although not definite, that this man acquired his infection as a result of exposure to poliomyelitis virus in the laboratory.

* During the 15 year period prior to 1930, the great majority of work on experimental poliomyelitis in the United States was carried out with strains of virus which were well established (through many passages) in the monkey.

2. Prior to his infection he was working with human infectious material and with strains of poliomyelitis virus in their early monkey passage.

3. Poliomyelitis virus was isolated in this case: from the throat (during life), and at autopsy from the central nervous system, the washed wall of the duodenum, mesenteric lymph nodes and from some of the right axillary lymph nodes. Attention is called to this last fact because just prior to his illness he sustained an injury to his skin on the right wrist.

4. Previous experiences, both published and unpublished, on the isolation of poliomyelitis virus from lymph nodes is reviewed and discussed in the light of the findings in the above case.

5. Histologic lesions of poliomyelitis were present in one anterior olfactory nucleus. Extensive lesions were present in the midbrain, pons, medulla and spinal cord.

6. The portal of entry of the virus was not determined.

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GYNECOMASTIA DUE TO MALNUTRITION

I. CLINICAL STUDIES*

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GYNECOMASTIA has been found associated with a wide variety of disturbances of the endocrine system, including atrophy^{11,30} and tumors of the testes,^{15,17,25} tumors of the adrenal cortex,^{32,48} hyperthyroidism⁴⁹ and tumors of the pituitary,³⁸ and has been induced by the administration of estrogen,¹⁴ androgen³³ and desoxycorticosterone.^{29,41} In the vast majority of cases reported, however, no obvious endocrine defects have been demonstrated.^{20,22,52,53} Nevertheless, there is ample clinical and experimental evidence to suggest that gynecomastia is usually hormonal in origin.

Recently we have seen a number of gynecomastias associated with malnutrition. Our interest in the relationship between nutrition and the hormones and in the possible rôle of the liver led us to study these cases. The present report is concerned with our clinical observations and the results of our investigation of the liver. Our hormone excretion studies will be reported in the following communication.

Material and Methods. Approximately 300 American soldiers, recently released from Japanese prison camps, were transferred to an Army hospital for further study and treatment in December 1945. They were taken prisoner in the Philippines during April and May 1942, and were released early in September 1945. Most of them

spent 2½ years in Filipino and 1 year in Japanese or Korean prison camps, where they lived on inadequate diets and suffered from severe malnutrition. In August 1945, food was dropped by parachute into some of the camps, but most of the men did not receive an adequate diet until they were released in September. Then they gained weight rapidly, so that by December signs of malnutrition and deficiency disease were absent.

On examination 36 of these men were found to have gynecomastia. In addition, there were 12 men who had had gynecomastia before admission to the hospital. These have been added to the series making a total of 48 cases. No case has been included that did not have a definite tumor mass in one or both breasts, or give a history of having had one. Many of the men had tenderness or fatty enlargement of the breasts without a palpable mass. Since pseudogynecomastia could not be ruled out in such cases, they have been excluded from consideration.

A detailed history of the diet, nutritional state, complicating diseases, breast symptoms and sexual activity was recorded in each case. A careful physical examination, with special emphasis on the condition of the breasts, liver and testes was performed. The breasts and testes were measured with a flexible centimeter rule. Testes smaller than 4 x 2.5 x 3 cm. were regarded atrophic.²³

A blood count, urinalysis, Kahn test and stool examination for ova and parasites were done routinely.

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The functional capacity of the liver was tested by a number of methods described elsewhere,²⁶ and the same criteria of abnormality were adopted:

One minute serum bilirubin	Over 0.2 mg. per 100 cc.
Total serum bilirubin	Over 1 mg. per 100 cc.
Thymol turbidity reaction	5 and over
Cephalin-cholesterol flocculation	1+ in 24 hours
	2+ in 48 hours
Quantitative urobilinogen excretion	Over 1.2 units in 2 hours in 2 out of 3 specimens
Total serum proteins	Under 5.5 gm. per 100 cc.
Bromsulphalein (5 mg./kg.)	6% retention in 45 minutes

Once gynecomastia occurred it usually persisted for a long period of time, unless there was an improvement in the diet. The severity of the condition, however,

The semen was examined in a small number of patients. It was collected in a small glass jar, diluted in a blood pipette and counted in a hemocytometer in the usual fashion.

Twenty-four hour urine specimens were collected for determination of 17-ketosteroid, estrogen, cortin and gonadotropin excretion. The specimens were kept refrigerated and were preserved with toluene. As soon as the collection was completed, the urine was acidified with dilute acetic acid and it was shipped to New Haven by express, a distance of 1200 miles.

fluctuated in a third of the cases. In some of these, relapses and exacerbations occurred spontaneously, but in others they appeared to be related to an improvement in the diet.

Tenderness of the breasts was the outstanding symptom in all but 2 cases. It was frequently so severe that these patients were unable to wear a shirt with comfort. The nipples were especially sensitive and were frequently more erect than normal. A few patients complained of spontaneous mild aching pain.

TABLE 1.—CLINICAL CHARACTERISTICS OF DIETARY GYNECOMASTIA IN 48 PRISONERS OF WAR

Onset		
During imprisonment (interval 4 to 40 mos, av. 15 mos)		33
After release (interval 2 wks. to 3 mos, av. 1.4 mos)		15
Duration		
Gynecomastia present 3 mos after release (duration 1 to 38 mos., av. 15.5 mos)		36
Gynecomastia cured 3 mos. after release (duration. 1 to 32 mos., av. 7 mos.)		12
Relapses and exacerbations		15
Following improvement in diet		7
While on deficient diet		8
Symptoms		
Tenderness		46
Pain		6
Secretion		7
Physical examination:		
Side: Bilateral		31
Unilateral		17
Glandular tumor mass (size: 1 to 4 cm., av. 2.6 cm., in diameter)		36
Tenderness (slight 13, moderate 11, severe 7)		31
Induration (slight 21, moderate 15)		36
Fatty enlargement of the breasts		23

Findings. Breasts. The clinical features of the gynecomastia observed are outlined in Table 1.

Gynecomastia usually appeared after prolonged malnutrition. In a third of the cases, however, the onset did not occur until shortly after return to a normal diet.

A definite secretion from the nipples had been noted by 7 patients, but in none could it be demonstrated in the hospital. It was described as "milky" in all but 1 and had been of sufficient volume to stain the underclothes.

The outstanding finding on physical ex-

amination was a mass of glandular tissue beneath the areola. The mass was usually discoid in shape, sharply demarcated and slightly to moderately indurated and tender. It was attached to the nipple, but was freely movable beneath the areola and over the underlying structures. It was often as small as 1 or 2 cm. in diameter, but it was usually surrounded by an appreciable deposit of fat, so that the contour of the breast resembled that of the female at puberty (Fig. 1). The areola occasionally exhibited an increase in pigmentation, but it was rarely marked in degree.

fibrous tissue, measuring 5 cm. in diameter and 1.7 cm. in thickness. On one side there was a depression from which fibrous bands radiated. Microscopically, it exhibited the typical changes described in other forms of gynecomastia.^{22,31,50} The principal findings were hyperplasia of the ducts and an increase in the periductile tissue. The ducts were increased in number, elongated and tortuous, and showed considerable branching. Their epithelial lining was thickened, and in some areas exhibited papillary growth into the lumen. Although no cysts were demonstrable, a number of the ducts were dilated and had



FIG. 1.—Case 23. Bilateral gynecomastia due to malnutrition.

Bilateral gynecomastia was much more common than unilateral. Frequently, however, the onset and clinical course differed on the 2 sides.

In 2 patients the axillary lymph nodes exhibited moderate enlargement without tenderness. Whether this lymphadenopathy was related to the associated gynecomastia could not be determined.

The glandular mass was excised for study in the patient illustrated in Figure 1. It shelled out of its fatty bed with ease and appeared to be a disk of fat and

thin walls. There was a great increase in the periductile tissue, which was composed of loosely arranged fibroblasts and fine fibrous strands in which were enmeshed a moderate number of lymphocytes and macrophages. The remaining fat and collagenous connective tissue, which comprised the bulk of the tumor, were not remarkable. There were no acini (Fig. 2).

Nutritional History. The essential data regarding nutrition are summarized in Tables 2 and 3.

As indicated in Table 2, the diets in

Filipino and Japanese prison camps differed, but both were equally deficient in protein, vitamins and calories.

The caloric deficiency was only moderate, but due to the heavy labor required of these patients and the frequent occurrence of untreated complicating disease the weight loss was marked.

dyspnea on exertion, which could be attributed to malnutrition, there were no outspoken cardiac symptoms. It is assumed that protein deficiency contributed to the edema, although no data on the level of the serum proteins during imprisonment are available.

As already indicated, signs of deficiency

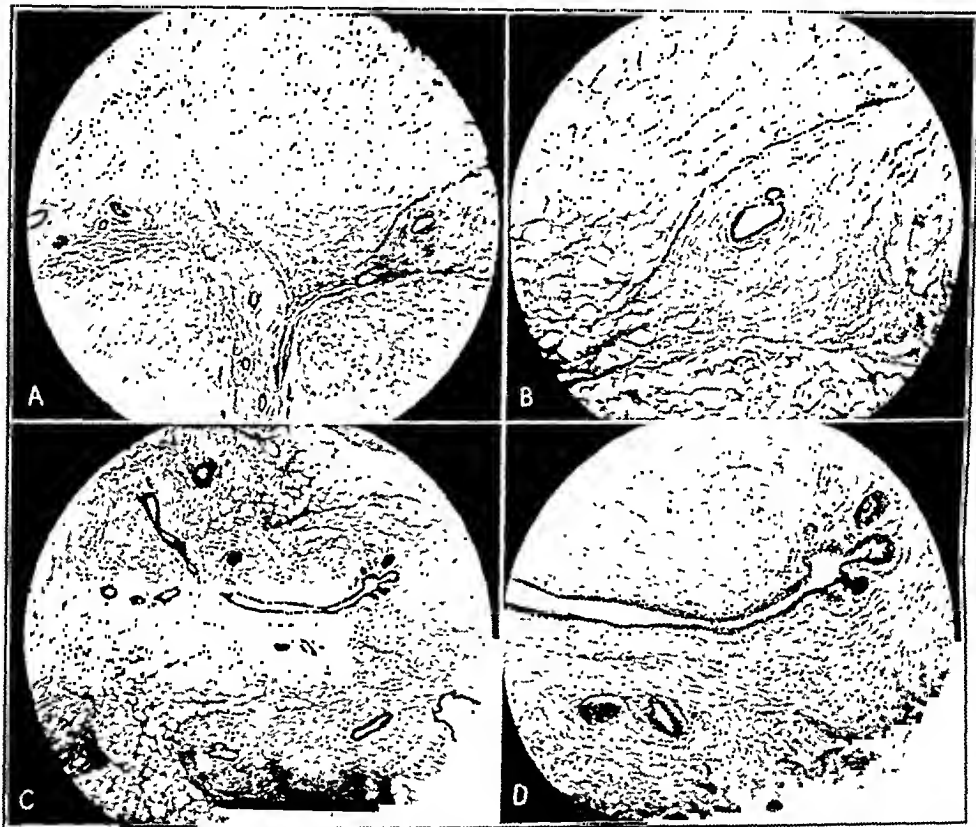


FIG. 2.—A, Normal male breast. Low power magnification. B, Normal male breast. High power magnification. C, Case 23. Dietary gynecomastia. Low power magnification. D, Case 23. Dietary gynecomastia. High power magnification.

Almost all of the group had severe beriberi, pellagra or scurvy in prison. Many were hospitalized for over 1 year. Specific treatment was inadequate, usually consisting of minimal supplement of vitamins and milk, and was rarely instituted until the patient was bedridden.

Beriberi was by far the most common deficiency disease encountered and occurred in all but 4 of the cases. It was usually manifested by both neuritis and marked edema. Except for weakness and

disease and malnutrition were lacking when these cases came under our observation. A few exhibited minor subjective sensory changes and minimal edema of the lower extremities. These failed to respond to intensive vitamin therapy. Exhaustive studies, including serum proteins, venous pressure, circulation time, electrocardiogram and Roentgen ray examination of the heart failed to disclose the etiology of the residual edema exhibited by 1 of these patients.

Chronic dysentery, chronic malaria and acute infectious hepatitis occurred in a high proportion of the cases during imprisonment. Intestinal parasites were very common. Although specific treatment was instituted in many cases before they came under our observation, half the cases still harbored 1 or more parasites as late as December 1945.

As already indicated, gynecomastia occurred after prolonged malnutrition, but in 17 cases it did not appear until shortly after the resumption of a normal diet. The latter group includes 2 patients who developed gynecomastia in prison following a temporary increase in the diet. In both instances gynecomastia subsided in several months, only to recur when a

TABLE 2.—CONTENT OF DIETS EATEN BY PRISONERS-OF-WAR WHO DEVELOPED GYNECOMASTIA

	Average daily intake			
	Protein (gm.)	Fat (gm.)	Carbohydrate (gm.)	Calories
Philippines (2 to 2½ yrs.)	43	7	353	1658
Japan (1 to 1½ yrs.)	41	8	397	1824

Content:	Philippines (gm./No. days)	Japan (gm./No. days)
Rice (polished)	480 to 520/day	280/day (Formosa)
Barley or millet	450/day (Japan)
Soybean	30/3 days
Bread	40/30 days
Meat	100/7 days	
Fish	30/7 days	30/7 days
Egg	30/30 days	
Milk (10% of patients)	30/day	
Vegetables: native spinach (tele- lium), sweet potato tops (com- ote), string bean leaves	100/day	
Radishes (dikon)	30/day
Seaweed	15/2 days
Potato	30/3 days
Fruit: bananas, mangoes, papayas, oranges, limes	1 to 3/7 days	
Tangerines, apples, pears	1/60 days

TABLE 3.—NUTRITIONAL HISTORY OF 48 CASES OF DIETARY GYNECOMASTIA

Average daily content of prison diet:	
Protein	42.0 grams
Fat	7 5 grams
Carbohydrate	375 0 grams
Calories	1735 0 calories
Weight loss:	
Average	61.1 lbs. (27.7 kg.)
Range	27 to 100 lbs. (12.3 to 45.5 kg.)
Nutritional diseases:	
Beriberi	44
With edema	38
Pellagra	38
Scurvy	27
Complicating diseases:	
Dysentery (unclassified)	34
Malaria	30
Acute infectious hepatitis	25
Intestinal parasites	23*
<i>Ascaris lumbricoides</i>	15
Hookworm	6
<i>Trichuris trichiura</i>	1
<i>Strongyloides stercoralis</i>	1
<i>Entamaba histolytica</i>	2

* Demonstrated in December 1945. Other data in table refer to conditions during imprisonment.

normal diet was resumed on release from prison.

The early and late effects of a good diet following prolonged malnutrition differed. In a general way it may be stated that it aggravated or precipitated many gynecomastias during the first 3 months, but that as dietary treatment was continued more and more cases were improved or cured.

As indicated in Table 4, the immediate effects of a normal diet were to precipitate or aggravate gynecomastia in half the cases. A much smaller group showed improvement during this period. In striking contrast were the effects of a normal diet at the end of 5 months. By then all but 2 of the gynecomastias were improved or cured. Four cases underwent spontaneous cure in prison before any improvement in the diet occurred.

made of the actual food intake, but we know it was poor in many instances. Digestive disturbances and abdominal distension were very common following the initial period of overeating, so that many patients ate sparingly at the hospital.

The effect on the recovery rate of gynecomastia of a high protein diet supplemented with 90 gm. of casein was studied in 16 patients. The diet was begun during the 4th month of treatment. When the effects were compared with those induced by the routine diet during the same period, no significant differences could be found.

Although multivitamin capsules were offered as part of the diet from the time of release, their content was so variable, and they were taken so irregularly that their effects could not be assessed. A group of 8 patients, therefore, was given

TABLE 4.—A COMPARISON OF THE EARLY AND LATE EFFECTS OF A NORMAL DIET FOLLOWING PROLONGED MALNUTRITION

<i>Early Effects (2 weeks to 3 months)</i>	
Gynecomastia precipitated or aggravated	25
Gynecomastia improved	14
No effect on breasts	9
Cases with gynecomastia when diet was started	27
Improved	14
Aggravated	8
Unchanged	5
Cases without gynecomastia when diet was started	21
Gynecomastia precipitated	17
No effect on breasts	4*
<i>Late Effects (5 to 7 months)</i>	
Gynecomastia improved or cured	42
Gynecomastia unimproved	2
No effect on breasts	4*

* Spontaneous cures before normal diet was resumed.

No data were available on the content of the diet eaten during the first 3 months following release from prison. It must have been high in protein, calories and vitamins, as the patients recovered their former weights and all signs of vitamin and protein deficiency disappeared rapidly.

At the hospital the usual diet for ambulatory patients, containing 80 gm. of protein and 3000 Cal., was offered to all but 16 of the cases. No measurements were

a large supplement of vitamin B complex† for 30 days at the end of the 3rd month of treatment. There was considerable improvement of the gynecomastia at the end of the period, but when the results were compared with those of a regular diet during the same period, no significant difference could be demonstrated.

Liver. The liver was investigated for abnormalities of structure and function which might be correlated with a disturb-

† Thiamin chloride 15 mg., riboflavin 9 mg., nicotinic acid amide 150 mg. and 9 brewers' yeast tablets daily.

ance of estrogen metabolism leading to gynecomastia. Our findings are summarized in Table 5.

More than a third of our cases exhibited hepatomegaly, impaired liver function or both. The interpretation of these abnormalities, with regard to their relation to malnutrition, is complicated by the fact that 25 patients had a history of acute infectious hepatitis in the past. A high proportion of individuals, presumably

mastia be related in point of time to the active stage of the disease.

Although the observed hepatomegaly was only moderate in degree, it is significant that in more than half the cases it was associated with tenderness. Only 3 of these 5 cases had a history of hepatitis.

Almost a quarter of the group exhibited impairment of liver function. As indicated in Table 6, the degree of impairment was always mild, and in only 3 cases was it

TABLE 5.—SUMMARY OF INVESTIGATION OF THE LIVER IN 48 CASES OF DIETARY GYNECOMASTIA

Hepatomegaly				9
With tenderness			5	
With impaired function			1	
Impaired function				11
Two or more tests abnormal			3	
Functional tests:				
	No. tests	Abnormal tests	Confirmed by other tests	Hepatomegaly
One minute bilirubin	35	0		
Total bilirubin	35	1	1	1*
Thymol turbidity	35	1	0	0
Ceph.-chol. flocculation	12	7	3	1*
Urobilinogen	8	3	2	1*
Serum proteins	30	0		
Reversal A/G ratio	30	1	1	0
Bromsulphalein	32	2	0	0
Spider nevi				7
With enlarged liver			1	
With impaired function			2	
Reticulated erythema				19
With enlarged liver			4	
With impaired function			3	
Relationship of abnormal findings to history of hepatitis:				
	Total (48 cases)	Hepatitis (25 cases)	No hepatitis (23 cases)	
Hepatomegaly and/or impaired function	19	13	6	
Hepatomegaly	9	5	4	
Impaired liver function	11	9	2	
Spider nevi	7	5	2	
Reticulated erythema	19	7	12	

* Case 11.

cured of this disease, exhibit similar residuals.²⁶ Significantly, half our cases with a history of hepatitis and only a quarter of those without such a history exhibited abnormalities of the liver. Nevertheless, in the latter group no cause other than malnutrition could be found for the observed hepatomegaly or impairment of function.

In none of the cases with a history of acute hepatitis could the onset of gyneco-

demonstrable by more than 1 test. However, it should be noted that the full battery of tests was not performed in every case. All but 2 of these cases had a history of hepatitis in the past.

The association of cutaneous spider nevi with liver disease, nutritional deficiency and pregnancy is well recognized. Recent work^{3,4,5} suggests that their occurrence is related to an increase in circulating estrogen.

A significant number of our cases had 1 or 2 spider nevi. They were located on the chest in 3 and at the base of the neck in 4 patients. Although 5 of these had a history of infectious hepatitis it is unlikely that the nevi were related to it. When spider nevi occur in infectious hepatitis, the disease is usually active and severe. It is more likely, therefore, that they were related to malnutrition.

15 seconds and reappeared when they were returned to the dependent position. There were no significant changes in the skin, nails or sweat glands. The appearance of the hands resembled that seen in *livido reticularis*.^{2, 43}

Of the 7 cases with spider nevi, 5 also showed palmar erythema, suggesting that the 2 conditions may be related. Significantly, hepatomegaly or impairment

TABLE 6—LIVER FUNCTION STUDIES

Case No *	1 min bilirubin (mg %)	Total bilirubin (mg %)	Thymol turbidity (units)	Cuph cholesterol flocculation	Urobilinogen† (units)	Serum proteins (gm %)	Serum albumin (gm %)	Bromsulph retention (%)	History of hepatitis	Hepatomegaly	Nevi	Palmar erythema
1	0.05	0.45	2	0				0	0	0	0	2+
3	0.07	0.15	2	2+/3+	0	7.03	3.45		+	0	+	0
5	0.07	0.55	1			6.10		0	+	0	+	0
6	0.07	0.15	4	1+/2+	0	6.28	3.90	0	+	0	0	0
7	0.05	0.10	4	2+/3+		6.70	3.60	1.7	+	0	0	0
9	0.15	0.75	3		0	6.80	3.70	7.5	+	+	+	1+
10	0.10	0.30	2			6.32	4.12	0	0	1+	+	2+
11	0.17	1.75	2	1+/2+	1.55			0	+	1+	+	0
12						6.06	3.69		+	0	+	1+
13	0.10	0.60	2	0		5.82	3.71	0	+	+	0	2+
14	0.07	0.45	1		1.40	6.70		0	+	0	0	1+
15	0.10	0.45	2			6.33	3.96		+	0	0	0
16	0.07	0.35	3	1+/3+	2.76	6.33		2.5	+	0	0	0
17	0.15	0.90	3			5.77	3.75	12.5	+	0	0	0
18	0.05	0.75	6			7.20	3.99	3.7	+	0	+	2+
19	0.05	0.35	3			6.50	4.10	0	+	0	0	2+
20	0.10	0.90	3			6.33	4.46	0	0	0	0	1+
21				±/2+		6.15			0	0	0	0
23						7.18	4.23		+	0	0	1+
24	0.07	0.40	3			6.45	3.99	0	+	0	0	1+
25	0.07	0.30	2	0		6.50	3.74	0	+	1+	0	0
26	0.05	0.25	4			6.25	3.64	5.0	+	0	0	0
27	0.07	0.45	3			6.67	3.61		+	0	0	0
28	0.07	0.55	1					0	+	0	0	0
29	0.05	0.75	3					0	+	1+	0	0
30	0.07	0.45	4			6.75	4.00	0	+	+	0	1+
31						6.17			+	0	+	1+
32	0.07	0.35	3			7.12	4.65	3	+	0	+	0
34	0.15	0.60	3		0			0	+	0	+	+
35	0.05	0.55	2	1+/3+		6.30	3.90	0	+	0	0	0
36	0.10	0.35	1					0	+	0	0	0
38	0.07	0.60	4	1+/2+		7.70	4.69	0	0	0	0	0
39	0.07	0.45	2			6.52		0	0	0	0	0
40	0.07	0.45	3					3.5	+	0	0	0
43	0.07	0.76	2		0	6.85	4.24	0	+	1+	0	0
45	0.17	0.35	2					0	0	0	0	0
46	0.10	0.50	1			7.00	4.24	0	0	0	0	0
47	0.05	0.25	2	±/1+				0	0	0	0	1+
48	0.20	0.45	1			7.00	4.15	0	+	0	0	0

* Cases 1 to 36 had gynecomastia when tests were performed

† Tenderness and hepatomegaly

‡ Values below 1.3 units recorded as 0 other values are highest of 3 specimens. Cases 36 to 48 had gynecomastia before admission to hospital

Palmar erythema occurs under the same conditions as spider nevi.^{3, 45} More than a third of our cases exhibited a striking bright reddish-purple mottling of the palms with a diffuse erythema of the fingertips. The mottling disappeared promptly when the hands were elevated for 10 to

of liver function occurred in 7 of the 19 patients with palmar erythema. Of those with impairment of function, all had a history of hepatitis, but 3 of the 4 cases with hepatomegaly had no such history.

Endocrine System. Clinical investigation disclosed significant changes in the genital system in an appreciable number of our cases. The other endocrine glands appeared to be normal clinically. The findings are summarized in Table 7.

Although the testes usually appeared

As indicated in Table 7, the spermatozoa were decreased in number and motility in released prisoners both with and without gynecomastia. There was a very poor correlation between the sperm count and the size of the testes or the state of libido and potency.

TABLE 7.—SUMMARY OF INVESTIGATION OF THE GENITAL SYSTEM IN 48 CASES OF DIETARY GYNECOMASTIA

Atrophy of the testes	15					
Enlargement of the prostate	2					
Sexual function:						
Loss of libido after imprisonment	45					
Persistence of diminished libido after treatment	13					
Diminished sexual potency after treatment	15					
Sperm counts (normal minimum values: 3 to 10 cc., 60 millions, 75% motile):						
<i>Prisoners With Active Gynecomastia</i>						
Case	Volume (cc.)	Sperm (millions)	Motility (%)	Atrophy of testes	Diminished libido	Diminished potency
15	4	37	75	+	+	?
19	6	42	50	+	0	+
20	4	14	15	0	0	0
27	7	160	90	0	0	0
<i>Prisoner With Gynecomastia in the Past</i>						
46	9	84	80	0	+	+
<i>Prisoners Without Gynecomastia</i>						
H.	7	63	75	?	?	?
R. W. G.	10	20 6	80	?	?	?
H. S.	5	20 1	50	?	?	?
R. A. Z.	5	12 6	50	?	?	?

normal, almost a third of them proved to be atrophic on direct measurement. There was no decrease in the size of the penis and the distribution of hair, contour of the body, texture of the skin and voice were within normal limits. Slight diffuse enlargement of the prostate was noted in 2 of the 6 patients examined.

Complete loss of libido occurred during imprisonment in all but 3 cases. A similar loss also occurred in most of the prisoners without gynecomastia. It took several months to develop (average 5.6) but the administration of an adequate diet effected a rapid return of libido, usually in a few weeks. Nevertheless an appreciable number of patients still had diminished sex desire after 3 months of dietary treatment. Furthermore, many of them noted loss of potency at this time, as indicated by a failure of erection, premature ejaculation or loss of orgasm.

Comment. From the evidence presented it seems reasonably certain that the form of gynecomastia described in this report was due to malnutrition. The only other etiologic factor that might be considered is acute infectious hepatitis, which occurred in 25 of our cases. Gilder and Hoagland¹⁸ have demonstrated an increase in estrogen excretion in this disease, and gynecomastia has recently been encountered as a complication.²⁷ Both the increased excretion of estrogen and the appearance of gynecomastia occurred during the active phase of the disease. In none of our cases could the onset of gynecomastia be related in point of time to the hepatitis. Furthermore, 23 cases of gynecomastia occurred in individuals with no history of hepatitis, so that it appears unlikely that hepatitis was the primary etiologic factor, although it can-

not be excluded as a contributing factor in some cases.

The mechanism by which malnutrition induced gynecomastia and the explanation for its occurrence both during malnutrition and following the resumption of a normal diet warrant further consideration.

The abnormalities of the liver and testes, demonstrated in a significant number of these cases, suggest at least 2 possible mechanisms: (1) malnutrition impairs the ability of the liver to inactivate estrogen and thereby induces hyperestrinism and gynecomastia; and (2) malnutrition depresses testicular function, either directly or through the pituitary, with the resultant decrease in androgen or "inhibin" activity leading to gynecomastia.

The relationship between gynecomastia and liver disease was noted first in cirrhosis.^{12,47} Estrogen is normally inactivated by the liver.⁵⁴ An increased excretion of estrogen, especially of the unconjugated form, occurs in cirrhosis complicated by gynecomastia.²¹ There is abundant evidence to indicate that estrogen plays an important rôle in the pathogenesis of gynecomastia. Indeed, some workers^{16,30} believe it is the major factor in all cases. An increased excretion of estrogen has been found in cases of gynecomastia associated with chorioepithelioma of the testes¹⁷ and carcinoma of the adrenal cortex⁴⁸ and gynecomastia has been produced by the administration of estrogen both in man¹⁴ and in experimental animals.^{16,31}

Experimental rats fed diets deficient in vitamin B complex develop a functional impairment of estrogen inactivation by the liver.^{6,7,8,44} There is some evidence to indicate that this occurs also in humans.^{9,10} Recently it has been found that the effects seen in rats are due to general malnutrition and not to a specific vitamin deficiency.¹³ A similar decrease in estrogen inactivation occurs in rats on cirrhosis-producing diets^{19,45} indicating the importance of protein deficiency. Unna and his associates⁵¹ have presented evidence to suggest that the liver requires an adequate supply of both protein and vitamin B to

maintain its function of estrogen inactivation.

A significant number of our patients exhibited signs of liver damage. Although antecedent hepatitis could not be excluded as an etiologic factor in some, no cause for liver damage other than malnutrition could be found in the remainder. Meienberg and Snell²⁶ have also noted liver damage in malnourished prisoners-of-war. These findings lend support to the hypothesis that the gynecomastia in our cases was due to an impairment of estrogen inactivation induced by malnutrition. The disturbance in estrogen metabolism which occurs in vitamin B deficiency is unaccompanied by histologic changes in the liver.⁸ Estrogen destruction is accomplished by an oxidative enzyme system.²⁴ Malnutrition may upset this mechanism by altering the internal chemical environment of the liver without inducing other structural or functional changes. Thus, the absence of overt liver damage in many of our cases does not exclude a functional derangement of estrogen metabolism.

Our patients lived on diets deficient in protein, vitamins and calories for a long time. The data do not indicate which of these factors was responsible for the gynecomastia. No special significance can be attached to our failure to demonstrate a curative effect of large supplements of vitamin B and protein, since these experiments were undertaken so late in the course of treatment.

The liver presumably requires one or more elements in the diet to maintain its function of estrogen inactivation. It is possible that in those cases in which gynecomastia was precipitated by a good diet, the requirement of these elements fell with the metabolic rate during malnutrition, so that an otherwise inadequate diet sufficed. During the initial period of restored nutrition, however, when the metabolic rate was rising rapidly, the requirement was so great that even the normal diet failed to meet it. A similar mechanism may operate in the hitherto

unexplained gynecomastias that occur occasionally in hyperthyroidism.⁴⁹

The 4 gynecomastias that recovered spontaneously during the state of malnutrition are of interest. MacDonald³⁴ has found that administration of estrogen to castrate rabbits induces hyperplasia of the breasts, but that if it is continued for over 100 days the breasts return to normal. Thus, spontaneous recovery in our cases may have been due to unusually prolonged estrogen activity.

The association of gynecomastia and atrophy of the testes is well recognized.^{11,30} It has been suggested that the testes inhibit growth of the breast in normal males³⁷ and androgen has been employed with some success in a few cases of gynecomastia.^{1,53} There is evidence, however, to contradict this hypothesis. Gynecomastia frequently does not respond to androgen therapy.^{42,50} An increase in androgen excretion has been reported in gynecomastia,⁴⁸ and injections of androgen have produced gynecomastia in humans³³ and in experimental animals.⁴⁵

Klinefelter and his associates²⁸ have recently described a number of gynecomastias with atrophic testes in which biopsies revealed hyalinization of the seminiferous tubules with normal appearing interstitial cells. They review the evidence for the existence of a second testicular hormone, X-hormone (inhibin), secreted by the seminiferous tubules, and suggest that in their cases gynecomastia was due to the normal growth-promoting effect of androgen on the breast, in the absence of the inhibiting effect of X-hormone.

The oligospermia and loss of libido and potency indicate that there was a decrease in both tubular and interstitial cell activity in our cases. If Klinefelter's hypothesis is correct, it is possible that gynecomastia occurred because X-hormone was decreased to a greater extent than androgen; furthermore, that in the gynecomastias that were precipitated by a good diet the return of androgen activity to normal was more rapid than that of X-hormone.

Testicular atrophy occurs in malnutrition³⁹ and severe liver damage.⁴⁰ It was probably due to malnutrition in our cases. The degree of liver damage we encountered appears to be too mild to account for testicular atrophy. There is some evidence that the effects of malnutrition on the testes are mediated through the pituitary,³⁵ although a direct effect cannot be excluded.

Our observations do not warrant any definite conclusions regarding the pathogenesis of gynecomastia due to prolonged malnutrition.

Summary. 48 cases of gynecomastia are presented with evidence to indicate that they were due primarily to chronic malnutrition. Clinical investigation revealed abnormalities of the liver and genitalia. The relationship of these abnormalities to malnutrition and their possible rôle in the pathogenesis of gynecomastia has been discussed. The findings do not warrant any definite conclusions regarding the pathogenesis of gynecomastia due to malnutrition.

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GYNECOMASTIA DUE TO MALNUTRITION

II. ENDOCRINE STUDIES*

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In the communication immediately preceding, the occurrence of gynecomastia in relation to severe malnutrition was described. It was suggested that derangement of liver function may have contributed to this lesion. The problem, however, seemed to be primarily one of endocrine imbalance, especially because testicular atrophy was noted. Accordingly determinations of 17-ketosteroids ("androgens"), estrogens, "cortins," and follicle-stimulating hormone in the urine were undertaken.

These determinations were made at a time when the subjects had returned to normal weight, and at intervals varying from 1 to 38 months after the onset of the gynecomastia. The object of the laboratory studies was to test the various hypotheses as to mechanism, which resolve themselves into 2 main categories as follows:

1. Malnutrition impairs the hepatic inactivation of estrogen and thus leads to hyperestrinemia.

2. Malnutrition depresses the pituitary, with secondary atrophy of the testes and resulting decrease in androgen excretion and possibly of "inhibin" activity.

Experimental Methods. Twenty-four hour urine samples were collected with toluene as a preservative, and immediately acidified to pH 6 with acetic acid. The urines were obtained from subjects who were patients in a military hospital and from civilian gynecomastics in New Haven. Control urine samples were collected from individuals in

3 categories, namely, (a) released prisoners-of-war without gynecomastia; (b) medical corps personnel from the same hospital, and (c) normal men and women from New Haven. The urines were extracted according to the scheme outlined by Pincus¹³ with minor modifications. Because the urines from military personnel were shipped by express over 1000 miles, special care was taken to compare control and test urines obtained under like conditions. The method of Cahen and Salter was used for the determination of 17-ketosteroids.¹ Cortins were determined by a modification of the method of Talbot.¹⁶ Estrogens were determined by bioassay, according to the modified Marrian procedure as described by Thayer and Doisy.¹⁷ In certain instances these estrogen values were confirmed by a chemical method developed in this laboratory. Follicle-stimulating hormone was estimated roughly by the method of Klinefelter, Albright and Griswold.⁸ Tests for liver function have been described in the communication immediately preceding.

Results. The data for 17-ketosteroids are illustrated in Figure 1 and Tables 1, 2 and 3.

Gynecomastia in Military Personnel. Although a few of the 27 values for gynecomastic patients were within the normal range for males, the group as a whole showed low values. When construed as an array of increasing values, the group constituted a statistical population which fell intermediate between those of normal males and normal females of the same age group (20 to 45 years). The respective mean values, expressed in milligrams per

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24 hours, were 8.4 ± 2.2 for females; 10.3 ± 2.9 for gynecomastic males, and 14.2 ± 4.8 for normal males. It will be observed that the values for normal males in New Haven were indistinguishable from the group obtained for controls in the Army camp. Statistical analysis by Miss Barbara Bartels showed, further-

tion of estrogens was made on castrated female mice by a bioassay procedure which is much less accurate than the chemical method used for 17-ketosteroids. Therefore, no great emphasis is placed upon absolute values, but rather the relative magnitude of the excretion was considered significant. It was quite clear, however,

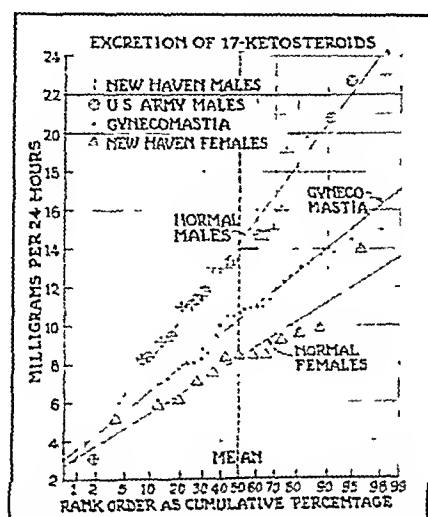


FIG. 1.—On the basis of 17-ketosteroid excretion, the cases of gynecomastia constituted a population distinct from either normal males or normal females.

TABLE 1.—URINARY EXCRETION OF TOTAL 17-KETOSTEROIDS IN NORMAL FEMALES

Subject	Age (yr.)	Rank (order)	17-Ketosteroids (mg. per 24 hr.)
A.	29	1	5.2
M. K.	29	2	5.9
M. M.	35	3	6.1
M. M. M.	32	4	7.1
B. M.	23	5	7.6
D. F.	25	6	8.4
A. M.	22	7	8.5
D. S.	28	8	8.5
B. B.	30	9	8.5
P. W.	39	10	9.3
S. T.	22	11	9.6
R. D.	28	12	9.9
M. B.	24	13	14.0

Mean 8.35 ± 2.24

more, that the population of gynecomastics was discrete from either the group of normal males or the group of normal females: the probability values, P , were both less than 0.01 that this discrimination was accidental.

As shown in Table 4, the excretion of "cortins" was normal. The determina-

tion of estrogens was low in the gynecomastic group as compared with simultaneous analogous determinations on normal controls. Moreover, chemical analyses for estrogens by a method developed in this laboratory yielded low results. The biologic data are presented in Table 4. No significant amount of unconjugated

estrogens could be detected, although at low excretion levels this determination has little significance. As regards the estrogen-androgen ratios, moreover, they were no higher than in the normal males. The normal ratios, as shown in Table 4, range from 0.11 to 0.74. The comparable range for the gynecomastias was from 0.05 to 0.76. Obviously there was no evidence of an estrogenic preponderance at the time these patients were studied.

In these cases, also, the excretion of 17-ketosteroids was low and the estrogen:androgen ratios were normal.

Discussion. Many theories have appeared in the last few years on the mechanism of gynecomastia.^{2,7,10,12} In this communication pertinent facts are presented in the form of hormonal values for a group of gynecomastia cases associated with malnutrition.

Beside gynecomastia, these patients

TABLE 2.—URINARY EXCRETION OF 17-KETOSTEROIDS AND "CORTINS" IN NORMAL MALES FROM ARMY AND CIVILIAN GROUPS

Subject	Rank (order)	17-Ketosteroids (mg. per 24 hr.)	"Cortins" (mg. per 24 hr.)
J. G. S.	1	3.1	0.63
R. B.*	2	8.3	1.17
E. M. K.*	3	8.4	0.73
R. O.*	4	9.2	0.66
N.*	5	9.5	0.14
B. G.	6	11.0	
J. H. C.*	7	11.1	0.60
S.*	8	11.4	0.68
B.*	9	11.8	0.24
O. K.	10	13.0	
W. W.	11	13.0	
S. K.	12	13.0	
Z.*	13	13.4	1.67
R.*	14	13.7	0.71
J. F.	15	14.0	
D. M.	16	14.0	
W.*	17	14.7	0.85
J. W.*	18	14.7	
V. D.	19	15.0	
E. R.	20	16.0	
R. M.	21	19.0	
E. Mc.	22	20.0	
T. S.	23	20.0	
R. C.	24	20.0	
G. K.*	25	20.8	1.06
S.*	26	22.7	1.14
W. S.	27	23.0	
Mean		14.2±4.8	0.79±0.37

* Army (14 cases).

As regards the follicle-stimulating hormone, no elevation above the normal excretion level could be demonstrated. Not much emphasis, however, could be placed upon this negative finding because the stability of the FSH was unknown under the conditions of the experiment.

Gynecomastia in Civilians. Both Tables 1 and 4 contain additional data obtained from a heterogeneous group of gynecomastias encountered in New Haven. None of them were associated with malnutrition.

showed testicular atrophy and low "androgen" excretion. Associated with these findings was a concomitant oligospermia and a diminution in potency. Unfortunately, it is not known whether these testicles showed the hyalinization of the tubular tissue described by Heller and Nelson.⁵ It is already established that low 17-ketosteroid excretion may follow either cachexia¹⁴ or liver damage.^{3,4} Both factors may have been operative in these prisoners-of-war. The finding of a dim-

inished 17-ketosteroid excretion, accordingly, raises the possibility that a decrease in androgens was responsible for the breast development. This theory has led some investigators^{6,18} to test the therapeutic use of testosterone in gynecomastia, but with conflicting results. The best evidence that

In addition to a marked tendency toward testicular atrophy in both groups, the liver is also suspect. In the malnourished group definite evidences of this has been recorded in the preceding communication. In addition, histologic examination of 2 cases has been reported by

TABLE 3.—GYNECOMASTIA—URINARY EXCRETION OF 17-KETOSTEROIDS AND "CORTINS" IN GYNECOMASTIA IN MILITARY AND CIVILIAN HOSPITAL PATIENTS

Case No.	Patient	Rank (order)	17-Ketosteroids (mg. per 24 hr.)	"Cortins" (mg. per 24 hr.)	Diameter of breast tumor (cm.)	Interval since onset of gynecomastia (mos.)	Atrophy of testes	Liver dysfunction
<i>Military Personnel</i>								
31	Nich.	1	4 1	0 95	3 5	29	0	
35	Tyr.	2	4 3	0 89	4 0	4	+	+
15	Hiet.	3	6 1	1 75	2 0	36	+	0
9	Fer.	4	7 3	0 21	3 5	33	0	+
32	Hop.	5	7 8	1 29	2 0	1	+	0
5	Cen.	6	8 1	1 48	2 5	4	0	0
23	Oliv.	7	8 1	0 83	4 0	36+	0	
39	DeG.	8	8 3	0 40	0	33	0	0
34	Str.	9	8 6	1 25	3 0	2	0	0
6	Chris.	10	9 5	0 41	3 0	3	0	+
18	John E.	11	10 1	2 15	2 0	4	+	+
25	Rog.	12	10 5	0 57	3 5	13	0	0
26	Shad.	13	10 5	1 95	2 5	1	0	0
11	Gim.	15	10 9	1 12	4 0	4	0	+
33	Alb.	16	10 9	0 48	2 0	36	+	
4	Bur.	17	11 0	0 53	2 0	3	0	
7	Dam.	18	11 0	0 40	2 0	25	0	+
10	Fitz.	19	11 4	1 93	2 5	3	+	0
13	Hay.	20	12 3	1 00	3 0	1	+	0
43	Sch.	21	12 6	0 22	0	33	+	0
14	Hilt.	22	13 1	0 73	4 0	2	+	+
16	Hop. C.	23	13 2	1 41	2 0	13	+	+
17	Imm.	24	13 7	2 36	3 0	38	+	+
19	John M.	25	13 8	0 53	2 0	13	+	0
46	Vand.	26	14 5	1 05	0	19	0	0
48	Horn.	27	15 0	0 61	0	12	+	0
Mean			10 3±2 9	1 02±0 60				
<i>Civilians</i>								
POP	Cartw.	1	2 2	0	..	1	0	?
BS2024	LaBr.	2	4 0	0 27				
S	Stew.	3	4 2	0				
POP	Seco.	4	5 4	0	5 0	24	+	0
PP 205	Spra.	5	7 8	0 37	0	
	Welc.	6	9 9	0 38	+	
Mean			5 6	0 17				

* Case numbers refer to patients discussed in the communication immediately preceding.

a diminished androgen output probably does not account for gynecomastia lies in the fact that gynecomastia has been induced by injections of testosterone¹⁰ and also that in some cases of gynecomastia an increased excretion of androgen has been demonstrated.¹⁵

Meienberg and Snell,¹¹ through whose courtesy we were able to examine their manuscript on "Nutritional Deficiency as a Probable Cause of Hepatic Damage in Repatriated Prisoners-of-war." Their biopsy specimens showed fatty infiltration and other evidence of liver impairment,

presumably transient in character. More-over, these authors studied 51 such patients who were repatriated prisoners-of-war, and found a high incidence of clinical and laboratory evidence of hepatic damage. Dietary deficiencies were considered as possibly responsible, in the absence of any evidence of the rôle of hepatotoxic agents or of systemic disease.

ponderance had passed before the mammary hyperplasia was observed. It might also be maintained that the urinary excretion of estrogens does not reflect adequately the concentration of circulating hormone. This latter supposition, however, appears contrary to the general experience in other physiologic and pathologic conditions involving estrogenic activ-

TABLE 4.—URINARY EXCRETION OF ESTROGENS IN GYNECOMASTIA

Case No.*	Patient	Rank (order in androgen table)	Total estrogens (mcg. per 24 hr.)	17-Ketosteroids "androgens" (mg. per 24 hr.)	Estrogen: androgen ratio
<i>Military Personnel</i>					
32	Hop.	5	0.6	7.8	0.08
13	Hay.	20	0.7	12.3	0.06
48	Horn.	27	0.7	15.0	0.05
11	Gim.	15	1.5	10.9	0.14
14	Hilt.	22	1.8	13.1	0.14
34	Strak.	9	2.0	8.6	0.23
18	John E.	11	2.4	10.1	0.24
26	Shad.	13	2.6	10.5	0.25
31	Nich.	1	3.1	4.1	0.76
15	Hiet.	3	3.1	6.1	0.46
6	Chris.	10	4.2	9.5	0.44
10	Fitz.	19	4.7	11.4	0.41
17	Imm.	24	4.7	13.7	0.34
Mean			2.5±1.4	10.2±2.8	
<i>Civilian Patients</i>					
POP	Cart.	1	2.1	2.2	0.95
S	Stew.	3	2.8	4.5	0.62
POP	Scø.	4	1.9	5.5	0.35 ⁷¹
PP 205	Spra.	5	0.9	7.8	0.11
Mean			1.9	4.8	
<i>Normal Controls</i>					
	Smi.	1	2.3	3.1 ⁷	0.74
	Kin.	2	1.6	8.4	0.19
	Nud.	3	2.2	9.5	0.23
	Rub.	4	4.2	13.7	0.31
	Wat.	5	9.0	14.7	0.61
	Klat.	6	8.6	20.8	0.41 ⁷²
	Sten.	7	2.4 ⁷³	22.7	0.11
Mean			4.3	13.3	

* Case numbers refer to patients discussed in the communication immediately preceding.

Although several theorists have proposed estrogen imbalance as a possible cause of gynecomastia, these patients showed a low urinary estrogen excretion. These low values were obtained through bioassay on castrated mice, and confirmed by a colorimetric method recently developed in this laboratory. Of course, it might be assumed that the estrogenic pre-

ity. With respect to a hypothetical preponderance of estrogen, it is striking that the ratio of estrogens to androgens is normal despite the low androgen values observed. In short, the normal estrogen: androgen ratio reflects a proportionate diminution in the excretion of both sex hormones. It is of interest that a heterogeneous

group of gynecomastias encountered in civilians without malnutrition showed essentially the same hormonal excretion and normal estrogen:androgen ratios.

The rôle of the pituitary in gynecomastia remains obscure. In Heller's cases of Sertolian atrophy there was a high excretion of follicle-stimulating hormone.⁵ Likewise, in the group of gynecomastias reported by Klinefelter, Reifenstein and Albright,⁹ an excessive excretion of follicle-stimulating was noted, namely, the characteristic "castration phenomenon." Our findings resemble those of both reports, except that no increase in FSH could be demonstrated. Obviously, a combination of quantitative data will be needed for the final solution of the mechanisms involved in various types of gynecomastia.

Summary. In 27 cases of gynecomastia of nutritional origin, determinations of urinary 17-ketosteroids, cortins, estrogens and follicle-stimulating hormone have been made.

Control studies were made on normal individuals from the military and civilian populations. In addition, cases of gynecomastia occurring in civilian life were studied.

As a group, the gynecomastics showed significantly lowered values for 17-ketosteroids. Estrogens were in the low normal range. "Cortins" were normal. No elevation of follicle-stimulating hormone was detected. The estrogen:androgen ratio was normal.

The findings distinguish this group from the gynecomastia of cirrhosis and acute hepatitis, but at the same time suggest that temporary derangement of liver function may play a prominent rôle in the pathogenesis of the lesion. A possible alternative explanation is that the pituitary-gonadic axis is primarily involved.

The group was not dissimilar to certain types of gynecomastia found in the civilian population.

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MILD RHEUMATIC REACTION IN COAST GUARD RECRUITS

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EACH winter and spring a high incidence of acute ankle arthritis has been noted at this Coast Guard Training station. Analysis of the 1945 outbreak leads to the conclusion that it is a mild manifestation of rheumatic fever. Of all cases of rheumatic fever in the 1945 epidemic, 54% ran a significantly similar course characterized by transient mild ankle arthritis with a paucity of other symptoms.

The clinical features are reported because this pattern of rheumatic reaction has not been described previously as frequent either in civilian life or military outbreaks.^{1,3,4,12}

CLINICAL FEATURES. Practically all the cases were in new recruits, men from widely separated regions of the country, experiencing barracks life for the first time, and under 19 years of age. Only 6 of 52 had been on the station over 21 days; only 4 had been in service over 90 days. Some patients would carry on with symptoms a few days before reporting ill; others would report early. There are probably unreported cases, in men who failed to report at sick call because they were able to carry on their duties.

Symptoms were first noted in the morning with ankle pain and disability, occasionally with fever and malaise. Examination showed redness, swelling, tenderness, and heat about one or both ankle joints. Signs of intra-articular fluid were definite in most cases. In addition, there was a periarticular soft, non-pitting induration of the adjacent skin and subcutaneous tissue. Signs and symptoms would fade in a few days. Ankle signs or symptoms lasted 1 day in 5 cases, 2 days in 23 cases, 3 days in 14 cases, 4 days in 3 cases, 6 days in 1 case and 7 days in 1 case. Telangiectasis and ecchymoses about the involved skin would usually be

evident on the 2nd or 3rd day of involvement and would disappear a day or 2 after subsidence of articular fluid. The highest emperature recorded was 103° F. Nine ran no temperature elevation; 4 were febrile for 6 days; the remainder were febrile less than 3 days. In 30 of 52, the maximum elevation was under 101° F.

Data from some cases are incomplete but all taken together confirm rheumatic involvement. When the 52 were analyzed carefully, 13 (25%) showed definite rheumatic stigmata as reported in Table 1. In 29 cases 1 or more ECGs were taken, with evidence of transitory carditis found in 5. Of 48 cases, in which 1 or more sedimentation rates were taken, values of over 15 mm. per hour were found in 44 and over 30 mm. per hour in 34. In 31 men questioned as to a recent respiratory infection, 22 gave positive answers. Of 40 questioned as to history of past rheumatic activity, 3 gave positive answers: 20 cases involved both ankles, 19 cases the left ankle alone, and 13 cases the right ankle alone.

Graphs show the monthly incidence of the ankle cases as compared with: (1) Rheumatic fever incidence. (2) Station (2) Station infirmary admissions for respiratory disease. (3) Station scarlet fever incidence.

The correlation between ankle incidence and the hospital rheumatic incidence is evident. The relation to the peaks of respiratory illness and scarlet fever incidence is definite.

It is probable that more rheumatic stigmata would have been found if facilities and time allowed for: (1) Longer follow-up; (2) repeated ECG studies; (3) anti-streptolysin titer studies.

Comment. This study describes a feature of the rheumatic state¹ not previously emphasized. In over 50% of the cases of our 1945 outbreak, signs and symptoms were confined to a few days of mild ankle arthritis with little systemic evidence of rheumatic fever. Follow-up and group study was required to establish the diag-

which are usually considered non-rheumatic." Diagnostic criteria of Jones⁷ (1944) are significant. He advises in cases of transient mild polyarthrititis, "If the patient has had tonsillitis, pharyngitis or even a cold in the past 2 or 3 months and serologic tests (such as antistreptolysin determination) indicate another recent

TABLE 1

- CASE 1. Aches in thighs, systolic murmur at apex.
 CASE 2. ECG changes of ST segment and T wave, knee pain.
 CASE 3. Subsequent spread to knee and wrist, 1° heart block, eventual aortic and mitral damage.
 CASE 4. Systolic murmur at apex, subsequent spread to knee, elbow and wrist.
 CASE 5. T wave changes, erythema marginatum.
 CASE 6. Stiffness of knees.
 CASE 7. 3° heart block, T wave changes, harsh apical systolic murmur, pain in heels.
 CASE 8. Stiffness and aches of calves and thighs.
 CASE 9. 1° and 2° heart block.
 CASE 10. Systolic murmur at apex, 1° heart block and spread to other joints.
 CASE 11. Aches in calves, thighs and back.
 CASE 12. Apical systolic murmur transmitted to axilla.
 CASE 13. Frequent nose-bleeds.

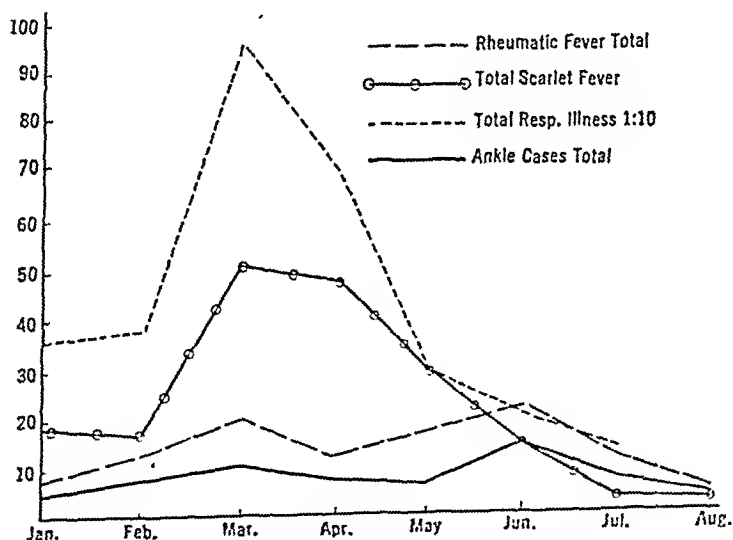


FIG. 1.—Monthly incidence of four items studied.

nosis which was often missed in past years. It is inferred that all epidemics include many cases of a mild type plus a possible group of subclinical cases. Study of cases of this type show the incidence of rheumatic fever to be higher than thought previously.

Findings may be correlated with those of Hall and Anderson⁶ (1943) who found a high incidence of rheumatic stigmata in detailed postmortem studies of "hearts

hemolytic streptococcus infection, the burden or proof rests with the physician who would not interpret such a syndrome as rheumatic fever. . . ."

The ECG reports and follow-up emphasize the fact that the mildness of arthritic symptoms give no indication of proneness to cardiac involvement. Treatment should be guided by our experience that in 43 patients who were kept at bed rest until sedimentation rates were normal, 29 re-

mained in bed over 7 days, while in 9 cases in which sedimentation rates were not done, only 1 was kept in bed over 7 days. Cohn and Lingg² (1943) have found that among patients first affected with rheumatic fever in adolescence, 40 % have polyarthritis alone.

Ankle swelling as one of the initial symptoms, but not as the sole arthritic symptom of classical rheumatic fever was noted in 75 % of the cases in the outbreak reported by Wheeler and Ingraham¹¹ (1945). They noted knee involvement in 80 %, arthritis of other joints less frequently. Localization to this joint alone in our series may result from peculiar conditions leading to the ankle strain in our recruits. Coast Guard trainees in their first few weeks undergo considerable strain which the orthopedist noted mainly in involvement of the plantar fascia and joints below the ankle. Trainees are on their feet 14 to 16 hours daily. They wear constrictive leggings of naval "boots." Static and traumatic factors may evoke local visible clinical reactions which might otherwise remain subclinical.

Experimentally, Vaubel¹⁰ found that intra-articular injection of horse serum, in a horse-sensitized rabbit, will cause arthritis of the injected joint and no reaction of other joints. However, exercise of a remote joint, under the same conditions will cause arthritis of this remote joint in addition.

The curves of incidence by month are in keeping with the findings of others,^{4,5,8} that in any outbreak of hemolytic streptococcal infections, a subsequent outbreak of rheumatic fever may be expected. The peaks of rheumatic fever incidence are delayed several weeks after the peaks of respiratory illness. Mathematical correlation between incidence is rough, varying from one-half to twice the number of scarlet fever cases which are manifest in some, but not all, of these epidemics, and from one-tenth to one-twentieth of the number of cases of all respiratory illness. The ankle cases emphasize the fact that many mild and subclinical cases are represented in each outbreak. The recent study of Bantz, Boisvert and Paul⁸ calls attention to mild and subclinical aspects of the "post-streptococcic state."

Summary. 1. A mild form of rheumatic fever with symptoms of ankle arthritis of a few days duration is described in 52 cases. A few had other mild signs subsequently.

2. These represent 54 % of all cases in one rheumatic fever outbreak, and have been seen frequently at this Coast Guard station in past years.

3. Local static and traumatic factors incident to recruit training may account for the high incidence of localization to ankles.

4. The incidence of mild manifestations in this epidemic was higher than that of frank, easily recognizable rheumatic fever.

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BLOOD PRESSURE STUDIES IN 100 CASES OF CORONARY OCCLUSION WITH MYOCARDIAL INFARCTION

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MANY observers have written on the course of the blood pressure following acute myocardial infarction, including Palmer,¹³ Gross and Engelberg,⁶ and Master *et al.*^{9,10} A later report by Master *et al.*¹¹ discusses the course of blood pressures before, during and after the attack.

The present report is an attempt to evaluate the influence of blood pressure on the incidence, clinical course and prognosis of coronary occlusion. The height of the blood pressure before the attack is compared with that during and subsequent to the acute episode. A similar study is made of the systolic, diastolic and pulse pressure in the hypertensive series. The influence of the changes and blood pressures on the subsequent symptoms, recurrences and life expectancy is discussed.

This study consists of detailed blood pressure observations on 100 cases of coronary occlusion with myocardial infarction at St. Luke's Hospital, New York City. Of these patients, 85 were studied from 1 to 10 years prior to the initial attack (a mean of 4 years), either on the wards or as out-patients.

The criteria used for making the diagnosis of the coronary occlusion with myocardial infarction were those enumerated by Shillito *et al.*¹⁶ fever, tachycardia, leukocytosis, increased sedimentation rate, blood pressure changes and electrocardiographic changes. As far as could be determined, the observers were dealing in each case with the initial attack. With the present study in view, each case was carefully observed; detailed clinical and laboratory evaluations were made. Serial electrocardiograms were taken until the infarct was thought to be healed.

Blood pressure readings were taken

daily on the majority of cases until stabilization or death. Following stabilization, the blood pressure readings were taken twice weekly and after discharge, at monthly intervals as often as possible. Follow-ups from 1 to 4 years were made on 64 of the 66 survivors consisting of a brief history and physical examination, blood pressure readings and electrocardiograms.

The criteria used for the diagnosis of hypertension were systolic pressure of 150 mm. of mercury or above and a diastolic pressure of 90 mm. or above. It has been conclusively demonstrated that the level of the blood pressure above 140 mm. systolic and 90 diastolic are abnormal at any age.⁴

Previous Hypertension. Of the 85 cases observed prior to the acute attack, hypertension was found in 74; 11 cases had normal blood pressures. There were 15 cases in which the blood pressures were unknown before the attack.

Of the 74 patients who had hypertension prior to the attack, 46 were of long standing. Its duration was unknown in 23 cases. In 5 cases the development of hypertension was observed during the year preceding the attack. The coincidence of hypertension and coronary occlusion have been reported between 30 and 75%.^{7,11,12,13} Hypertension has been found to be definitely higher in patients with this condition than in the general population.² In the present series, the incidence of hypertension was 74%.

Of the 34 patients who died of the acute episode, 24 (71%) were known to have had hypertension prior to the attack. This incidence of hypertension in the fatal series is roughly equal to the incidence of hypertension in the entire series: 71%

for the fatal series; 74% for the entire series. This is in agreement with most writers who find no relation between hypertension and mortality rate.^{3,5,12,17}

There were 72 males and 28 females in this series. Hypertension was present in 48 (66%) of the males and 28 (85%) of the females. Its incidence increased with age.

Past History. Over half of the hypertensives gave a past history of angina, dyspnea, or decompensation. These symptoms were more prevalent in those who survived the initial attack than those who succumbed. In general, their onset was more recent but of greater severity in the fatal group. There were 7 cases of diabetes mellitus in the fatal group and 2 cases suggestive of cholecystitis. There were 3 cases of diabetes, 3 with symptoms of cholecystitis and 2 cases of polycythemia vera, in the non-fatal group. The majority of patients with normal blood pressure gave no past history of hypertension, angina, dyspnea or decompensation.

the patients had hypertension. Of the known hypertensives, 39 (53%) had blood pressures within hypertensive levels on admission (see Table 1).

In the fatal series, 18 (68%) showed hypertensive levels at the initial readings; 2 (9%) had tension within normal limits; 6 (23%) had hypotensive blood pressures.

This is to be contrasted with the survival group in which 27 (46%) gave hypertensive readings, 23 (39%) were within normal range and 9 (15%) showed hypotensive blood pressures.

Thus, in the fatal series, over two-thirds of the cases showed an initial hypertension following the acute attack, while only one-fourth showed hypotension. In the survival group, less than one-half had hypertension at the onset and less than one-sixth had hypotensive blood pressures.

Initial Blood Pressure During Attack as Compared With Blood Pressure Before Attack. Of the entire group, 63% showed an initial fall of blood pressure on admission as compared with readings taken before the onset of the attack (Table 2);

TABLE 1.—ACUTE ATTACK (85 CASES) ANALYZED ACCORDING TO INITIAL BLOOD PRESSURE AND SURVIVAL

Initial blood pressure	Survived 59		Died 26		Total 85	
B.P. 150/90 mm. or above	27	46%	18	68%	45	53%
100/60 to 145/85 mm.	23	39%	2	9%	25	29%
100/60 mm. or below	9	15%	6	23%	15	18%

Present Illness. In the hypertensive series, 24 (32%) died of the initial attack. On admission, 83% of these had symptoms of marked severity. Of the 50 hypertensives who survived, approximately 50% had symptoms of marked severity.

The severity of the hospital course roughly paralleled the symptoms on admission. The hypertensive fatal group had the stormiest course, while in the non-fatal hypertensive group, one-half had a stormy course and one-half had a course of mild to moderate severity. The majority of cases with normal blood pressure had symptoms of only moderate severity.

Initial Blood Pressure During the Attack. Prior to the onset of the attack, 74% of

32% showed no change. There was an initial rise in blood pressure over the previous readings in 5% of the cases, all of which were hypertensives prior to the attack. Only 1 of this last group survived. This phenomenon has been observed by others.^{8,18} It may occur with the onset when the infarction is associated with severe pain.

Of the hypertensive fatal group, 20 (76%) showed an initial fall in blood pressure, the fall in the majority of the cases remaining within hypertensive limits. In this group, 3 patients had a rise in blood pressure and 3 had no change.

In the survival group, 58% showed a fall in blood pressure as compared with

previous readings, whereas 40% showed no initial change. A rise in blood pressure occurred in 1 case.

Blood Pressure Subsequent to Attacks. Although only 63% of the cases showed an initial fall in blood pressure, all cases showed a fall at sometime during the illness (Table 3). Frequently, however, the fall remained within hypertensive limits. If this did not occur on the 1st day, it usually occurred on the 2nd or 3rd. There were 2 cases in which the blood pressure did not fall until the 4th and 7th days respectively, shortly before death.

There was considerable variation in the response of blood pressures following the immediate or delayed fall (Table 4). Of those who succumbed to the attack, the largest percentage (67%) showed no return in blood pressure. The tension in these cases remained at lower levels than the initial reading until death. Of the fatal group, 17% had an early return to hypertensive levels. In this latter group, the pressures had all returned to their former levels within 10 days of their falls, with the exception of 1 case, in which the

TABLE 2.—ACUTE ATTACK (85 CASES)—INITIAL BLOOD PRESSURE AS COMPARED WITH PREVIOUS BLOOD PRESSURE

Initial blood pressure	Survived 59	Died 26	Total 85
B.P. rose	1 2%	3 12%	4 5%
B.P. fell	34 58%	20 76%	54 63%
B.P. unchanged	24 40%	3 12%	27 32%

TABLE 3.—CHANGE IN BLOOD PRESSURE—HYPERTENSIVE SERIES (74 CASES)

Acute attack	Survived	Died	Total
Initial fall (within 24 hours)	14 58%	36 72%	50 68%
Delayed fall (within 7 days)	7 29%	13 26%	20 27%
Initial rise	3 13%	1 2%	4 5%

TABLE 4.—HYPERTENSIVE SERIES (74 CASES)—COURSE OF BLOOD PRESSURE FOLLOWING INITIAL FALL

Course of blood pressure	Survived	Died	Total
Early return to hypertensive levels (1 week)	10 20%	4 17%	14 19%
Late return to hypertensive levels (4 months)	15 30%	0 0%	15 20%
No rise in B.P.	0 0%	16 67%	16 23%
Rise to normal levels	24 48%	1 4%	25 34%
Initial rise in B.P.	1 2%	3 12%	4 4%

The fall in pressure following coronary occlusion has always been considered one of the primary signs. The fact that it did not always fall immediately has been pointed out by a number of observers. Shillito *et al.*¹⁶ found that a fall in systolic blood pressure usually occurred early, although sometimes it was delayed for 24 hours. This fall was not invariably observed being absent occasionally when the infarct was small and the degree of shock slight. Master *et al.*¹¹ found that the fall frequently was not great in the first 24 hours. The pressure fell to 100 mm. or less in only 9% of their cases on the 1st day. Allen¹ noted that a week often elapsed before significant fall became evident.

blood pressure returned to normal but not to the previous hypertensive level.

In the 4 cases in which the blood pressure was initially elevated above the pre-attack levels, the pressure rapidly fell to hypotensive levels within the first 24 hours. In the 1 case that survived, the pressure fell to hypotensive levels within the first 24 hours, but then returned to normal rapidly and never reached its former hypertensive level. The 3 other cases had a rapid fall in their tensions following the initial rise and death ensued within 48 hours.

All cases in the survival group had a rise in blood pressure after the initial fall. Of these cases, 25 (50%) showed a return to the original hypertensive levels, 10

(20%) returned within 1 week, whereas 15 (30%) returned within 4 months. By the end of the 2nd year, 58% of those followed had regained their original hypertension, while 42% remained free of hypertension.

Palmer¹³ found that more than one-half of the patients had developed hypertension within 1 year after the attack. The number with hypertension then increased year by year until the incidence of hypertension reached 72% which was the same as before the attack. In Master's¹¹ series, hypertension returned in two-thirds of the cases. One-third of this series permanently lost hypertension.

taken prior to the attack, a tabulation was made of the average changes in systolic pressures, diastolic pressures and pulse pressures.

In those who survived, the systolic blood pressures fell more than the diastolic. The systolic pressure fell on an average of 36 mm., whereas the diastolic pressure fell 24 mm. In contrast to this in the fatal group, the fall in both systolic and diastolic pressures were greater than the systolic. In this series, the average systolic drop was 48 mm.; the diastolic 60 mm.

In the survival group, the average pulse pressure was 60 mm. before the attack.

TABLE 5.—SYSTOLIC BLOOD PRESSURE IN HYPERTENSIVE PATIENTS PRIOR TO ACUTE ATTACK

Systolic blood pressure		Survived		Died	
150 or over	43	57%		32	43%
160 or over	25	48%		27	52%
175 or over	10	42%		14	58%
185 or over	5	25%		15	75%
190 or over	4	22%		14	78%
200 or over	3	21%		11	79%
210 or over	2	14%		12	86%
215 or over	0	0%		9	100%

TABLE 6.—DIASTOLIC BLOOD PRESSURE IN HYPERTENSIVE PATIENTS PRIOR TO ACUTE ATTACK

Diastolic blood pressure		Survived		Died	
90 or over	43	57%		32	43%
100 or over	23	44%		29	56%
110 or over	8	29%		20	71%
120 or over	2	13%		13	87%
130 or over	0	0%		6	100%

Systolic Blood Pressure Prior to the Attack. A direct relationship existed between the height of the systolic blood pressures prior to the attack and the number of deaths. As the height of the systolic blood pressure increased above 150 mm., the fatalities increased (Table 5).

Diastolic Blood Pressure Prior to the Attack. An increase in diastolic pressure above 90 mm. prior to the attack was associated with a similar rise in deaths (Table 6).

Average Changes in Systolic Blood Pressure, Diastolic Blood Pressure and Pulse Pressure. In those cases in which there was a fall in the blood pressure during the attack as compared with readings

After the attack, it had decreased to 49 mm., a fall of 11 mm. In the fatal series the pulse pressure prior to the attack was considerably greater, being 77 mm. Following the attack, it fell to 51 mm., a fall of 26 mm. Thus, the average fall of pulse pressure was well over twice as great in the fatal group as it was in the survival group.

By this comparison, it is seen that the fall of both systolic and diastolic blood pressures was greater in the fatal group than in the survival group. In the fatal group, the fall in diastolic pressure was greater than the fall in systolic. The converse was true in the survival group in which the systolic fall was the greatest.

The pulse pressures, both prior to and after the onset of the attack, were greater and decreased more in the fatal group than in the survival group.

The greater falls in systolic, diastolic and pulse pressures in the hypertensive fatal group were due to the higher average pressures prior to the attack.

Symptoms 1 Year After the Attack. One year after the initial attack, 12 patients who had regained their original hypertension were compared with 12 patients whose hypertension had never returned.

The hypertensives whose blood pressure had not returned complained of a greater variety of symptoms including dyspnea, angina, fatigue and syncope. Those whose hypertension had returned complained of fewer symptoms but these were of greater severity. In this latter group, there were 4 individuals with decompensation, while in the group which did not regain hypertension, there was only 1 case of decompensation.

Electrocardiograms. No difference was found in the follow-up between the electrocardiograms taken on individuals with hypertension or those with normal blood pressures with respect to changes due to myocardial infarctions. Reversion to normal occurred in the same amount of time and in the same number of cases for those with hypertension as to those with normal blood pressures.

Recurrences. All cases having recurrences within 1 year of the initial attack had been hypertensive originally. Only 50% of the patients in this series had hypertension at the time of the second attack. There was no difference in the survival rate between those who had recurrences with normal blood pressures and those with hypertension at the onset of the second attack. Decompensation was more frequent in those individuals whose hypertension persisted. All of the recurrence group showed residua by electrocardiogram with the exception of 1 case.

The idea was formerly expressed that recurrences occurred with greater frequency in patients who regained their

hypertension after recovery from the first attack, than in those whose blood pressure remained normal. Allen,¹ and Palmer¹⁴ regarded the prognosis as better in those who regained their hypertension. Gross and Engelberg,⁶ and Master *et al.*¹¹ could find no effect of hypertension on the duration of life or frequency of heart failure following the attack. In Bland and White's³ 10 year follow-up, no striking effect of hypertension on the status during the first few years following the attack was noted but the added burden on the heart over a period of years was suggested by the relatively few patients with hypertension who survived the 10 year period.

In this series, no correlation could be made between recurrences and early return (within 10 days of the attack) or delayed return (within 4 months of the attack) of blood pressure to hypertensive levels. An equal number of cases who did not regain hypertension had the recurrence as those whose hypertension did return. After the initial attack, an individual was just as likely to have a recurrence whether or not the blood pressure returned to its original hypertensive level.

Summary. One hundred cases of coronary occlusion were studied with reference to the effect of the attack on the blood pressure, and the influence of the resultant blood pressure on the incidence, clinical course and prognosis.

Conclusions. 1. The incidence of antecedent hypertension is greater in individuals having coronary occlusion than it is in the general population (74% in this series).

2. There is no relation between antecedent hypertension and the mortality rate in coronary occlusion. The incidence of hypertension was 71% in the fatal group and 78% in the non-fatal group. However, in the hypertensive group, the mortality was directly proportional to the degree of hypertension.

3. Hypertension at the onset of the attack is a common finding (53% in this series) and occurs more frequently in the

fatal group (68%). Hypotension in the initial reading is a comparatively infrequent finding (18% in this series).

4. A fall in blood pressure usually occurs following coronary occlusion. The fall often remains within hypertensive limits. It may be immediate or delayed as long as 7 days after the attack.

5. An early return of blood pressure to normal or pre-occlusional hypertensive levels is a good prognostic sign. The blood

pressure usually does not return to its former levels in the fatal group.

6. The number of survivors who regain their original hypertension increases with the time elapsed after occlusion; 58% had regained their hypertension by the 2nd year.

7. After recovery from the initial coronary occlusion, the height of the blood pressure has no effect on the frequency of recurrence or ultimate prognosis.

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SPECIFIC DYNAMIC ACTION AS A MEANS OF AUGMENTING PERIPHERAL BLOOD FLOW

USE OF AMINOACETIC ACID*

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NUMEROUS agents have been employed for the purpose of increasing blood flow to the peripheral vessels. The status of vasodilator drugs has been summarized by Sir Thomas Lewis,²⁰ *i. c.*, "There are no known substances that can be safely used to produce an adequate and sufficiently persistent dilatation. There is no known remedy of this kind so persistently potent as warming of the body, and this is simple, economical and safe." Heat may be applied externally directly to the extremities, or remotely to abolish vasomotor constriction by reflex vasodilatation.¹² Internal heating, *i. c.*, increase in heat production, likewise has been used to increase peripheral blood flow, employing artificial fever or administration of foreign proteins such as typhoid vaccine^{7,27} or by means of thyroid extract to elevate the metabolic rate. Local heating of the affected parts, fever therapy, and thyroid extract have no place in the treatment of arteriosclerotic peripheral vascular disease, and may produce undesirable effects. While these measures increase peripheral blood flow, they increase the metabolism of the peripheral tissues as well, so that the net effect may be a decrease rather than increase in the efficiency of the peripheral circulation.

In the present investigation utilization has been made of specific dynamic action

to increase heat production in the body. It is well known that following a protein meal a considerable and sustained increase in the metabolic rate occurs. A peak increase averaging 20% above the basal level is attained between the 3rd and 5th hour, and an appreciable elevation of metabolism is still present after 7 hours.¹ The specific dynamic action, of proteins is due almost entirely to a few amino acids, notably glycine (aminoacetic acid), alanine, phenylalanine and tyrosine. The increase in heat production occurs chiefly in the liver. This is indicated by the absence of specific dynamic action after hepatectomy, by perfusion experiments, and by measurement of oxygen consumption of individual organs.²⁹

A study was carried out, extending preliminary observations,¹⁶ to determine to what degree the dissipation of this excess heat might be attended by changes in blood flow to the extremities. A linear correlation has been found to exist between the metabolic rate and peripheral blood flow over a wide range of metabolic levels in subjects with hyperthyroidism²⁵ and myxedema.²⁶ Significant increase in blood flow, both to upper and lower extremities has been shown to occur following ingestion of a protein meal, accompanying an increase in metabolic rate.³

Twenty gm. of glycine dissolved in 200

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to 300 cc. of water or milk* were administered in 25 subjects in 26 experiments in the basal state. Observations were made of oxygen consumption, skin temperature of toes, fingers and forehead, oscillometric pulsation in the calf and forearm, and quantitative blood flow as determined with the venous occlusion plethysmograph. Skin temperature was measured with the Leeds-Northrup potentiometer in the basal state and over a period of 4 hours following administration of glycine. Observations on the skin temperature were made before determination of oxygen consumption, and under conditions of approxi-

and a hand plethysmograph in 2 experiments. The findings are summarized in Tables 1 to 3.

Oxygen Consumption. The average maximal increase in oxygen consumption above the basal level in 18 cases studied was 18.4%. There was considerable individual variation, which may have been due in part to differences in the rate of intestinal absorption of glycine. Four subjects, including a case of myxedema, failed to exhibit a significant rise in oxygen consumption, following ingestion of glycine. The maximal increase in oxygen consumption was 52%.

TABLE 1.—AVERAGE CHANGES IN OXYGEN CONSUMPTION AND SKIN TEMPERATURE FOLLOWING GLYCINE (20 Gm.)

	Cases studied (18) (%)	Normal subjects (11) (° C.)	Peripheral vascular disease (4) (° C.)
Oxygen consumption . . .	+18.4		
Skin temperature:			
Toe	+4.0	+2.3
Finger	+2.8	+2.2
Forehead	+1.7	+0.8

TABLE 2.—COMPARISON OF SKIN TEMPERATURE CHANGES FOLLOWING GLYCINE, POSTERIOR TIBIAL NERVE BLOCK AND ALCOHOL

	6 cases		4 cases	
	Glycine (° C.)	Nerve block (° C.)	Glycine (° C.)	Alcohol (° C.)
Toe	+5.7	+4.5	+3.8	+1.2
Finger	+2.3	-0.2
Forehead	+2.4	+1.2

mately constant environmental temperature (22° C.±1.3°), with the extremities exposed for a period of 20 minutes before readings were made. Comparison was made with the effect on skin temperature of post-tibial nerve block in 6 cases and of 2 ounces of whiskey in 4 cases. The observations on nerve block and alcohol were carried out on different days than the glycine experiment. In 11 experiments on 10 subjects blood flow was determined by means of the venous occlusion plethysmograph. A foot plethysmograph was employed in 9 of these experiments

Skin Temperature. An increase in temperature of the toes occurred in all 11 cases with no impairment of peripheral circulation studied, and in 3 of 4 cases with peripheral vascular disease. Only 1 subject studied failed to exhibit a rise in temperature of the toes. In this case there was advanced bilateral peripheral vascular disease with acute right popliteal occlusion. The temperature of the fingers similarly increased in 14 of 15 cases. Forehead temperature increased in 6 of 9 cases tested. Excluding the 4 cases with peripheral vascular disease, the average

* In the initial experiments glycine in water was employed. Due to the sickening sweet taste of glycine which caused nausea and vomiting in an appreciable number of cases, particularly on protracted use, various compositions employing glycine with agents directed to overcome these distress provoking effects were tried. Mixtures of glycine and unsweetened cocoa, and also glycine and urea, with flavoring agents, prepared and supplied through the courtesy of the Medical Research Division of Sharp & Dohme, Inc., were found to be very satisfactory.

rise in temperature at the toes was 4°C. , at the fingers 2.8°C. and at the forehead 1.7°C. Significant increase in the skin temperature occurred within 1 hour after ingestion of glycine with maximal rise between the 2nd and 3rd hour.

The effect of glycine was compared with posterior tibial nerve block in 6 cases. In these subjects the average increase in toe temperature was 5.7°C. with glycine and 4.5°C. following nerve block. Comparison was made with the effect of alcohol in 4 subjects. In all these the increase in temperature in the toes was significantly greater with glycine than after alcohol (2 ounces of whiskey in basal state). The average change in tempera-

tively was 31.7°C. , 33°C. and 33.1°C. These temperatures indicate the maximal vasodilatation. According to Montgomery *et al.*,²³ "In the normal subject when vasodilatation is complete the skin temperature of the digits will rise to a level between 31° and 34°C. "

Oscillometric Readings. The amplitude of oscillometric pulsation in the calf increased in 8 of 11 subjects with no peripheral vascular disease. The average change for this group of 11 subjects was an increase in pulsation of 25%. No increase in oscillometric pulsation was observed in 3 cases with peripheral vascular disease, although significant rises in skin temperature occurred in 2 of these subjects.

TABLE 3.—CHANGES IN BLOOD FLOW (VENOUS OCCLUSION PLETHYSMOGRAPHY) AND OXYGEN CONSUMPTION FOLLOWING INGESTION OF GLYCINE (20 GM.)

Case	Blood flow (cc./min./100 cc. limb volume)		% change	Oxygen consumption		
	Basal flow	Maximal flow following glycine		Basal	Maximal	% change
1. J. R. D. . . .	3 32	4.84	+45 8			
2. R. G. . . .	2 70	4 02	+48 9	208	270	+27 4
	1 98	3.26	+64 6	233	300	+28 8
3. E. M. . . .	1 15	2 25	+95 7	200	255	+22 5
4. F. S. . . .	0 89	1 39	+56 2	245	260	+ 6 1
5. N. S. . . .	2 18	1 54	-29 4	190	200	+ 5 3
6. M. S. . . .	3 05	3 53	+15 7	191	210	+10 0
7. M. P. . . .	1.42	2.74	+93 0	305	300	- 4 9
8. L. G. . . .	3 48	4 96	+42 5	212	238	+12 3
9. B. S. . . .	3.02	3.80	+25 8	208	240	+15 4
10. H. S. . . .	4 14	3 13	-24 4	285	355	+24 6

ture at the toes was $+3.8^{\circ}\text{C.}$ with glycine, $+1.2^{\circ}\text{C.}$ with alcohol; at the fingers $+2.3^{\circ}\text{C.}$ with glycine, -0.2°C. with alcohol; and at the forehead $+2.4^{\circ}\text{C.}$ with glycine and $+1.2^{\circ}\text{C.}$ with alcohol. The initial temperature of the forehead was higher than the extremities. Following glycine a definite trend toward equilibration of temperature of the toes, fingers and forehead occurred. Thus, in 6 cases with no peripheral vascular disease, in whom the skin temperature changes at toes, fingers and forehead were recorded, the average initial temperature at the toes, fingers and forehead respectively was 26.4°C. , 28.8°C. and 31.4°C. Following glycine the average maximal temperature at toes, fingers and forehead respec-

In the forearm an increase in amplitude of pulsation following glycine was noted in 6 of 11 subjects. The average increase in this group of 11 cases was 33%.

Plethysmographic Studies. Venous occlusion plethysmography was carried out in 5 experiments on 4 normal subjects, in 1 case of myxedema, and in 5 subjects with peripheral vascular disease (Table 3). The latter included 3 cases with arteriosclerotic peripheral vascular disease, 1 case with thromboangiitis obliterans, and 1 case of scleroderma with the Raynaud syndrome. Blood flow through the hand was studied in 1 of the normal subjects (Case 1) and in a subject with scleroderma (Case 9); in the remaining a boot foot plethysmograph was employed. The technique em-

ployed and method of calculation of blood flow were as described by Abramson.² Observations were made in the recumbent position, obviating the effect of gravity, with a constant temperature foot bath of 31° C. and an occlusion pressure of 60 mm. Hg. A Brodie bellows and ink writing high speed kymograph recording system were used for recording; 12 to 15 records were made in each period of observation and the results averaged in calculating blood flow.

The control blood flow was determined in all subjects in the basal state following which 20 gm. of glycine, mixed with unsweetened chocolate or urea to neutralize the sweet taste, were administered in a glass of milk. Observations were made at $\frac{1}{2}$ hour periods to a maximum of 3 hours following ingestion of glycine. Although the specific dynamic action of glycine persists for 5 to 7 hours, it was not expedient to extend the experimental period beyond 3 hours because of increasing discomfort that attends prolonged confinement in the plethysmographic apparatus.

An increase in blood flow was observed in 8 of the 10 cases studied. Blood flow was not significantly affected until 1 hour following ingestion of the glycine, with maximal increase usually attained after $1\frac{1}{2}$ to 3 hours. In 2 subjects (Cases 5 and 10), a fall rather than rise in blood flow occurred. One of these (Case 5) was a subject with myxedema produced during thiouracil treatment of angina pectoris. In this case the oxygen consumption failed to rise appreciably, indicating a lack of specific dynamic action. This may have been due to delayed intestinal absorption of glycine, for impairment of intestinal absorption is known to occur in myxedema. A decrease in blood flow occurred in 1 other subject (Case 10), who had previously undergone sympathectomy for Buerger's disease. In this subject peripheral blood flow to the extremity tested was already presumably at its maximal value. Dilatation of the remainder of the peripheral vascular bed with redistribution of the peripheral blood

flow, attending a rise in oxygen consumption of 24.6 %, may have been responsible for a decrease in blood flow to the foot in this case.

A quantitative parallelism between the changes in oxygen consumption and peripheral blood flow could not be demonstrated in these experiments. In 1 subject with arteriosclerotic peripheral vascular disease (Case 7) a marked increase in peripheral blood flow occurred without any rise in oxygen consumption. In this subject it is probable that the initial metabolic rate was not determined in a fully basal state since the initial oxygen consumption was unusually high. It is of interest that the claudication time of this subject was almost doubled following ingestion of glycine in dosage of 20 gm.

Additional observation was made in 1 subject with peripheral vascular disease (Case 6) of venous filling time on dependency after elevating the extremities. In the basal state the veins began to fill in the right foot at 10 seconds with full filling at 90 seconds, while in the left foot initial filling of the veins was noted at 55 seconds with full filling at 150 seconds. Three hours after glycine administration initial filling of the veins of both feet occurred immediately on dependency, with full filling at 15 seconds in the left foot and 30 seconds in the right foot.

Comment. Observations with the techniques employed, *i. e.*, skin temperature, oscillometric readings and plethysmography indicate that effective peripheral vasodilatation can be accomplished by ingestion of glycine. The skin temperatures attained, fully equivalent to those resulting from nerve block, indicate maximal vasodilatation. The vasodilating action of alcohol is not only less in duration, but is less in degree than that produced by glycine. Abramson and co-workers⁴ found whiskey, in doses of 60 to 80 cc. to have little or no effect on blood flow in the leg. Horton *et al.*¹⁸ observed no change in the skin temperature of the feet following alcohol. With larger doses (4 to 6 ounces) Montgomery²² found sig-

nificant increase in blood flow to the toes, but this dose is not practical as a therapeutic procedure.

Neither Abramson and co-workers,⁴ nor Montgomery²² in testing a wide variety of preparations recommended for peripheral vascular disease, found any to be efficacious in increasing blood flow to the lower extremities. Intravenous hypertonic saline, which has been advocated as a therapeutic measure, was found by

attributed to an increase in blood volume²³ and decrease in blood viscosity.²⁴ Wilhelmj, Bollman and Mann³⁰ observed that intravenous hypertonic saline significantly increases heat production equivalent to 30 to 50% of the specific dynamic action of glycine. Physiologic saline had no effect. The increased peripheral blood flow observed in certain cases with intravenous hypertonic saline may be due to an increase in heat production in the body.

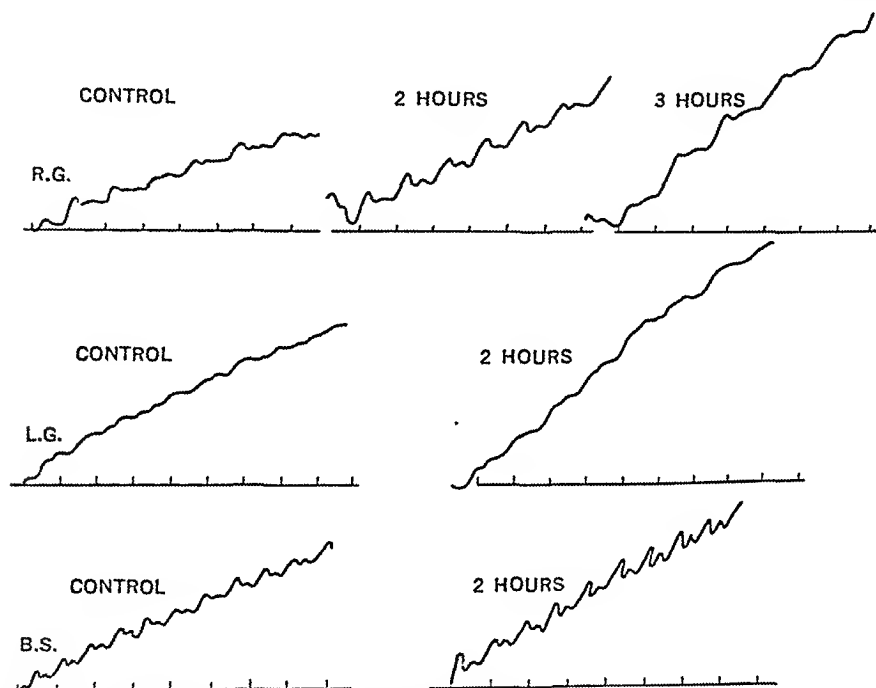


FIG. 1.—Plethysmographic tracings following ingestion of glycine (20 gm.). R. G., normal subject; L. G., arteriosclerotic peripheral vascular disease; B. S., scleroderma with Raynaud syndrome. Time is indicated on abscissa in seconds. Ordinate indicates limb swelling (arterial inflow). Following application of venous occlusion after glycine, the rate of limb swelling (arterial inflow) is increased, as indicated by the steeper slope of the curves. The individual pulse amplitude likewise is augmented.

Abramson *et al.*,⁴ and Friedlander and co-workers¹³ to augment blood flow to the lower extremities in an appreciable number of cases. The duration of increased blood flow to the feet was found to outlast the period of injection in only 3 of 14 cases and in these 3 subjects the increased flow to the feet persisted for an average period of 80 minutes.⁴ The mechanism of action of hypertonic saline in increasing peripheral blood flow has not been explained. It has been variously

similar to the mechanism of increased blood flow resulting from the specific dynamic action of glycine.

Increase in peripheral blood flow can be accomplished not only through peripheral vasodilatation, but by an increase in cardiac output. The increased blood flow observed with glycine is to be attributed in part to this factor. There is a linear relationship between the cardiac output and the metabolic rate.^{11,19} Ingestion of food causes a significant increase in the

cardiac output extending over several hours.^{14,15} Herrick *et al.*,¹⁷ employing the thermostromuhr method in dogs, found, concurrent with a generalized increase in circulatory flow during digestion, an increase in blood flow in the femoral artery as high as double the basal value during the 3rd hour of digestion. The plethysmographic tracings reproduced in Figure 1 demonstrate not only a steeper slope of limb swelling on application of venous occlusion following ingestion of glycine, but also heightened amplitude of the individual pulse waves, indicative of augmented flow.

Apart from the action of therapeutic agents such as glycine on peripheral blood flow, it is appropriate to consider possible effects on local tissue metabolism. The relation of glycine to muscle creatine metabolism has been the subject of extensive study, and several authors have reported favorable results with the employment of glycine in muscular dystrophies^{6,9,21} in simple muscular fatigue¹⁰ and in increasing the work capacity of normal individuals as determined by ergometric performance.⁵ However, reports that feeding glycine increases the creatine content of muscle tissue have not been regularly confirmed,⁸ nor has its application in improving muscular performance met with general acceptance. It appears possible that some of the therapeutic benefit claimed for glycine in muscular disorders may be due to increase in peripheral blood flow rather than a specific effect on creatine metabolism.

Summary and Conclusions. The effect of ingestion of 20 gm. of glycine on peripheral blood flow was investigated in 25 subjects; including 9 cases with peripheral vascular disease, employing the techniques of skin temperature, oscillometry and venous occlusion plethysmography.

The author is indebted to Doctor B. S. Oppenheimer for the loan of the plethysmographs employed in this study.

A rise in surface temperature was observed in the 3 regions tested, *i. e.*, toes, fingers and forehead. A significant increase in the temperature of the toes occurred in 11 normal subjects tested, and in 3 of 4 cases with peripheral vascular disease. The temperatures attained, fully equivalent to the effect of posterior tibial nerve block in 6 cases in which comparison was made, indicate maximal vasodilatation. The rise in temperature exceeded the effect of alcohol both in extent and duration in 4 cases in which comparison was made between the ingestion of glycine and 2 ounces of whiskey.

Oscillometric pulsation in the calf increased in 8 of 11 normal subjects, but no appreciable increase was observed in 3 cases with peripheral vascular disease.

Blood flow to the extremities, as determined by venous occlusion plethysmography, was increased in 8 of 10 subjects examined, including 4 of 5 cases with peripheral vascular disease. The average increase in blood flow was 62% in the normal subjects, 30.5% in the cases with peripheral vascular disease.

The increase in blood flow is an accompaniment of increased heat production with attendant peripheral vasodilatation and increased cardiac output resulting from the specific dynamic action of glycine. The average maximal increase in oxygen consumption above the basal level in 18 cases studied was 18.4%, the greatest individual rise 52%. The effect of glycine on oxygen consumption and on peripheral blood flow is manifest in 1 hour and is maximal after 2 to 3 hours. The specific dynamic action of glycine persists for a period of 5 to 7 hours.

It is concluded that the ingestion of glycine provides a simple physiologic means to accomplish an effective and sustained increase in peripheral blood flow.

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AN EVALUATION OF IMMUNE SERUM GLOBULIN AS A PROPHYLACTIC AGENT AGAINST HOMOLOGOUS SERUM HEPATITIS*

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HEPATITIS resulting from the parenteral introduction of an icterogenic agent, presumably a virus, in blood, plasma or serum, has been a major problem in World War II. With the expanding use of pooled blood and plasma this problem has not been solved by the cessation of hostilities. This homologous serum hepatitis is difficult, if not impossible, to differentiate clinically, from infectious (epidemic) hepatitis. It has, however, a longer incubation period, approximately 2 to 5 months, in contrast to approximately 2 to 5 weeks in the case of infectious hepatitis. It is not highly infectious in the usual sense of the term, in that no conclusive evidence thus far has been obtained of the infectivity of nasopharyngeal secretions, urine or stools from such patients, and secondary or contact cases have been rare. It is acquired, apparently, by the parenteral introduction of the etiologic agent, whereas in infectious (epidemic) hepatitis this appears to be a far less common mode of transmission. In contrast to serum hepatitis, infectious (epidemic) hepatitis is readily transmitted by fecal contamination and secondary or contact cases are not rare. Also, a lack of cross-immunity between 1 strain of serum hepatitis virus and 1 strain of infectious (epidemic) hepatitis virus has been demonstrated.⁵

The administration of gamma globulin has apparently established yet another difference. It is with this feature that the present study deals.

In January 1945, Stokes and Neefe⁶ reported favorable results from human immune serum globulin (gamma globulin) prophylactic therapy during an epidemic of infectious hepatitis in a summer camp for boys and girls. Of 331 persons, 53, who at the time showed no signs of the disease, were given gamma globulin intramuscularly. An arbitrary dosage of 0.15 cc. per pound of body weight was employed. The results, which were statistically significant, indicated that gamma globulin is capable of preventing or attenuating infectious (epidemic) hepatitis when administered to exposed persons during the incubation period of the disease.

In a study carried out among troops in the Mediterranean Theater of Operations in the fall of 1944, and involving 2 epidemics, Gellis, Stokes and others^{1,2} found gamma globulin in doses as small as 0.06 cc. per pound of body weight to be effective in the prevention of infectious (epidemic) hepatitis. The signs and symptoms of the disease in all 3 epidemics were similar.

Irrespective of possible etiologic differences, gamma globulin was apparently of

* This investigation was carried out in collaboration with the Commission on Measles and Mumps, Army Epidemiological Board, Preventive Medicine Service, Office of The Surgeon General, Washington, D. C.

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equal effectiveness in all 3 outbreaks of infectious hepatitis.

In an outbreak of infectious hepatitis in a home for children in New Haven, Havens and Paul⁴ gave prophylactic doses of 0.08 cc. of gamma globulin per pound of body weight by intramuscular injection. It was concluded that gamma globulin, when given during the incubation period, preferably earlier than 6 days before the onset of symptoms, was an effective prophylactic measure against infectious hepatitis.

An increasing incidence of hepatitis, presumably of the homologous serum type, among battle-incurred casualties prompted an evaluation of gamma globulin as a prophylactic and attenuating agent against this disease. This study was begun at England General Hospital, on April 3, 1945. The subjects were battle casualty patients who had received blood or plasma or both at the time of injury. It was among these patients that practically all the cases of hepatitis were appearing.

Method of Study. A team consisting of 1 medical officer, 2 nurses, and a ward technician, was organized to conduct the actual administration of the gamma globulin. The entire patient population of the hospital was surveyed and all those who were admitted prior to April 3, 1945, and were under treatment as battle casualties and had received transfusion of blood or plasma or both at the time of injury were selected. In order to detect early cases of the disease a specimen of urine was obtained from each patient of this group, and subjected to both the methylene blue test and the Harrison spot test for bile pigment. Patients in whom these tests were negative were selected for the study. Patients who gave a history of having had jaundice, also those who developed hepatitis within 10 days after receiving the gamma globulin, and those in whom more than 5 months had elapsed between the time the transfusion was given and the onset of hepatitis, were excluded from the series. Alternate patients were given a single dose of 10 cc. of gamma globulin, intramuscularly, while the alternating patients, not so treated, were used as controls.

During the period between April 3 and May 28, 1945, immune serum gamma globulin (human) (Army Medical Supply Catalogue Stock No. 1605500) manufactured by Firm A which obtained the plasma from inhabitants of the Far West and Northwest United States, was used. Following May 28, the study was continued using a product manufactured by Firm B, which obtained plasma from inhabitants of the eastern section of the United States.

Results. There was a relatively low incidence of hepatitis in the treated group in contrast with the controls in the early stages of the study. The reason for this is not entirely clear, but it appears most probable, in the final analysis, that a lag in the appearance of the disease was produced by the globulin therapy. That this retardation of the onset of the acute phase of the disease was the only effect of the single doses of globulin is suggested by the similarity of the clinical features of the disease in the globulin-treated and in the control groups.

An evaluation of the results up to and including Oct. 23, 1945, shows that of the 2406 patients who received gamma globulin, 29 (1.2%) developed hepatitis. Of the control group of 2374 cases, 23 (0.9%) developed hepatitis.

With regard to the number of days between the last transfusion of blood or plasma and the onset of hepatitis in our cases, a comparison of the data in Tables 1 and 2 shows that in the group injected with gamma globulin (Table 1) the shortest period was 47 and the longest 147 days, the average being 103 days, whereas in the control series (Table 2) the shortest period was 43 and the longest was 133 days, the average being 87 days. In Case 16 2 transfusions were given, one 114 days prior to onset of hepatitis and a second 66 days prior to onset of the disease.

With regard to the number of days between the injection of gamma globulin and the onset of hepatitis we find that in the treated group the period varied from 15 to 113 days with a mean of 52 (Table 1) as compared with 11 and 95 days and a

TABLE 1.—DATA ON GLOBULIN-TREATED PATIENTS WHO DEVELOPED HEPATITIS*

Case	No. days between onset of hepatitis and last blood or plasma transfusion	No. days between injection of gamma globulin and onset of hepatitis	No. days of jaundice	No. days for drop of jaundice from peak	Highest icterus index
1	58	16	3	3	28
2	74	21	21	Jaundice started on furlough	
3†	47	28	3	3	6
4	74	36	19	7	27
5	108	16	72	44	115
6	126	27	19	6	26
7	103	25	40	30	46
8	23	19	70	28	33
9	114	42	55	49	52.5
10	123	61	21	13	31
11	106	67	38	28	36
12	120	33	28	19	24
13	105	80	16	13	37
14	131	101	23	23	41
15	111	96	23	17	58
16	140	66	33	22	87
17	147	112	Still jaundiced	..	87
18	87	80	22	10	41
19	89	25	28	20	65
20	81	35	21	7	26
21†	123	64	3	3	8
22	80	58	48	13	48
23	75	60	Still jaundiced	..	64
24	89	53	34	20	48
25	142	88	30	14	43
26	95	63	18	14	31
27	90	32	31	29	26
28	145	15	Still jaundiced	..	55
29	105	113	Still jaundiced	..	48
	Av. 103	Av. 52	Av. 29	Av. 17	Av. 42

* The first 17 patients received gamma globulin prepared by Firm A, whereas the remaining 12 were given the product of Firm B.

† These cases filled all the criteria of hepatitis without jaundice.

TABLE 2.—CASES OF HEPATITIS APPEARING IN THE CONTROL SERIES

Case	No. days between last blood or plasma transfusion and onset of hepatitis	No. days between date designated as control and onset of hepatitis	No. days of jaundice	No. days for drop of jaundice from peak	Highest icterus index
1	83	11	16	5	25
2	85	25	26	8	16
3	91	20	18	12	40
4	68	39	13	7	51
5	108	35	11	10	25
6	61	12	43	35	74
7	112	44	5	Jaundice started on furlough	
8	94	27	35	No data	100
9	87	19	50	33	31
10	92	34	9	6	11
11	72	43	13	5	15
12	76	44	15	13	30
13	87	50	8	11	11
14	133	55	47	42	150
15	117	95	12	9	25
16	114	94	12	8	25
17	43	15	23	14	20
18	66	16	38	28	67
19	63	12	37	39	13
20	71	30	79
21	83	32	27	17	45
22	82	13	26	13	27
23	56	20	4	Died	51
	Av. 84	Av. 34	Av. 23	Av. 17	Av. 42

mean of 34 days elapsing between the date patients were designated as controls and the appearance of hepatitis in the untreated group (Table 2).

One patient of the control group died on the 4th day of illness. In view of the death occurring in the control series, no value can be attached to the figures concerning length and degree of jaundice.

The therapy was identical for treated and control patients. The management of hepatitis will be the subject of a subsequent publication.

In addition to the data presented here it has been the impression at 3 large general hospitals in this Service Command (New York, New Jersey and Delaware) that the practice of giving a single injection of 10 cc. of gamma globulin to battle casualty patients, begun on June 12, 1945, has not been effective in reducing the incidence of serum hepatitis resulting from the parenteral injection of whole blood, serum or plasma.

In contrast to the previous findings of Grossman, Stewart and Stokes³ concerning the use of gamma globulin at the McCloskey General Hospital in the prevention of homologous serum hepatitis, the incidence of hepatitis in the 2 groups reported here was not significantly different. The only discernible difference between the method of study and the cases selected in the 2 hospitals was the injection of 2 doses of gamma globulin (10 cc.) at an interval of 1 month at the McCloskey General Hospital as opposed to a single dose of gamma globulin (10 cc.) at the England General Hospital. The lower incidence of hepatitis in the injected group, as compared to the control group during the earlier part of the study at the England General Hospital at first suggested that the final results would be similar to those at the McCloskey General Hospital. That such was not the case, when the final results were tabulated, indicated that a considerable lag had occurred in the onset of hepatitis in the injected group. This lag is demonstrated by the fact that the average number of days from the injection

of globulin to the onset of hepatitis was 52 days; whereas in the control group the onset of hepatitis averaged only 34 days from the time they were designated as controls. The significance of this difference is also confirmed by the fact that the average intervals between the time the 2 groups received blood or plasma as battle casualties and the time they were injected with globulin or designated as controls were almost identical.

From statistical calculation there is approximately 1 chance in 400 that the lag, apparently resulting from the globulin injection, is not significant. In view of the significance of delay in the onset of hepatitis, apparently due to the injected globulin, the possibility is also apparent that an additional injection of globulin, as carried out at the McCloskey General Hospital might have actually prevented the occurrence of hepatitis in a certain number of the injected group at the England General Hospital even though the single dose failed to alleviate the course of the disease.

Another difference between the studies at the two General Hospitals is the strikingly higher total incidence of hepatitis at the McCloskey General Hospital. Because such hospitals differ considerably in the types of cases distributed to them, the incidence of hepatitis might vary considerably. Nevertheless, the high incidence of hepatitis at the McCloskey General Hospital, well above that recorded elsewhere, raises the possibility that both serum hepatitis and infectious (epidemic) hepatitis may have occurred simultaneously at the time of the study. If this were true, the low incidence in the injected group at that hospital presumably would have resulted from the demonstrated effectiveness of the gamma globulin from the American Red Cross pools in preventing infectious (epidemic) hepatitis. However, an acceptance of this explanation for the difference in results of the two studies would require a further explanation of the absence of hepatitis from the control group

of casualties at the McCloskey General Hospital, which did not receive blood or plasma, since at this Hospital the occurrence of hepatitis appeared to be associated almost exclusively with such transfusions.

Considerable evidence is accumulating which indicates antigenic differences between agents responsible for the two types of hepatitis. The possible differences in antibody content of the globulin used at the two hospitals must also be considered.

Neutralization tests conducted by Gellis, Neefe, and Stokes, which are as yet incomplete (to be reported), have yielded no satisfactory evidence to date of antibodies in the gamma globulin used against one agent of serum hepatitis.

The present report, together with certain additional data obtained in the same Service Command, suggested that a single injection of the gamma globulin used, although apparently delaying the onset, did not protect completely against homologous serum hepatitis, in contrast to the previously demonstrated value of a single injection (10 cc.) of similar globulin in protecting against infectious (epidemic) hepatitis. From these studies, and those conducted at the McCloskey General Hospital, there is evident need for further investigation of the value of repeated doses of gamma globulin from pooled plasma in serum hepatitis.

Summary and Conclusions. 1. A single dose of 10 cc. of immune serum gamma globulin, given intramuscularly to each of 2406 battle casualty patients who had received transfusions of blood or plasma, or both; within the previous 6 months, failed to reduce the incidence of hepatitis, presumably of the homologous serum type. Twenty-nine (1.2%) of these patients developed hepatitis in contrast to 23 (0.9%) in 2374 similar patients used as controls.

2. No difference was noted in the relative lack of effect of immune serums collected in the Eastern United States, and that collected in the Far West and North West United States in preventing homologous serum hepatitis.

3. The administration of the single dose of 10 cc. of globulin apparently retarded the onset of the acute phase of hepatitis by an average period of 18 days, a delay which is statistically significant.

4. The ineffectiveness of immune serum gamma globulin in a single intramuscular dose of 10 cc. for preventing homologous serum hepatitis presents another apparent difference between this disease and infectious (epidemic) hepatitis.

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HISTAMINE ANTAGONISTS

IV. PYRIDIL-N'BENZYL-N-DIMETHYLETHYLENEDIAMINE (PYRIBENZAMINE) IN SYMPTOMATIC TREATMENT OF ALLERGIC MANIFESTATIONS

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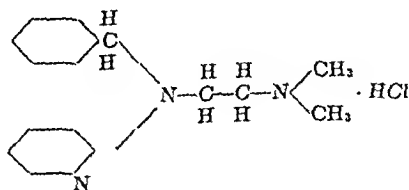
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THE rôle of histamine liberation as at least a part of the mechanism of anaphylactic shock, first suggested by Dale and Laidlaw⁵ in 1911, has had ample confirmation in subsequent years.⁷ The suggestion by Lewis¹³ that some allergic manifestations may be due to a similar histamine release has led to partial supportive evidence for this concept. The attempt to alleviate the symptoms due to histamine intoxication in anaphylaxis and allergy by the administration of the anti-histamine enzyme, histaminase, has resulted in failure.¹⁵ This has been due mainly to the fact that the prolonged incubation and close contact of histaminase and histamine required for the destruction of the latter cannot be duplicated *in vivo*.

In recent years considerable effort has been exerted in the attempt to develop synthetic chemical substances which would antagonize or annul the action of histamine, with the hope that they would display also an antianaphylactic and anti-allergic action.⁹ Among others, substances used and found either insufficiently active or too toxic were the amino acids: arginine, histidine and cysteine.¹² French experimenters demonstrated that certain synthetic compounds had such antihistaminic action. However, their first compounds, thymoxyethyldiethylamine and N-phenyl-N-ethyl-N'-diethylethylenediamine,¹⁷ were too toxic for both animal and man. Later, analogues of these

compounds (N'phenyl-N'benzyl-N-dimethylethylenediamine and N-p-methoxybenzyl-N-dimethylaminoethyl amino-pyridine), apparently possessing a high degree of antihistaminic, anti-anaphylactic and anti-allergic efficiency,¹¹ were prepared.

The present paper deals with the activity of a compound recently developed in this country, based on a chemical modification of the previously mentioned French histamine antagonists. This substance is Pyridil-N'benzyl-N-dimethylethylenediamine hydrochloride (Pyribenzamine).*



According to Mayer and his associates¹⁴ this drug has a high efficiency in the inhibition of histamine and anaphylactic reactions. These claims have been confirmed by us in experiments with guinea pigs. The results of these experiments as well as other experimental data in man will be reported elsewhere. Here we wish to present primarily the therapeutic action of this drug in allergic conditions.

Procedure. Most of the patients selected for this study were chronic cases, who had been under our observation for some time prior to this therapeutic trial. Their behav-

* Supplied by the Ciba Pharmaceutical Products, Inc.

ior to the usual palliative measures as well as their reliability in interpreting symptoms were known to us. Single observations were not trusted. Only those patients in whom periodic administration of the drug alleviated the symptoms while discontinuance of the therapy resulted in a recurrence were considered as benefited. This scheme was followed even in the acute cases. The patient was asked to report frequently for observation, and his history as well as the physical findings were checked on each visit.

The medication was given orally in 50 mg. tablets, preferably not on an empty stomach. Children tolerated 50 mg. doses well, while in infants 10 to 20 mg. doses were used. In most instances 4 doses of 50 mg. were administered daily; in some it was found necessary to give the medication every 3 or 4 hours. In others, 100 mg. doses 4 times daily were required. We were dissuaded from trying larger amounts by the impression that they were not tolerated well. In several instances, such as in nocturnal nasal blocking or in the prevention of the scratching in atopic dermatitis during sleep, only a bedtime dose of the drug was employed.

THERAPEUTIC RESULTS. The results of the therapeutic trials are listed in Table 1. In all instances where benefit was obtained it was limited to symptomatic relief for several hours following each dose. In 21 out of 27 cases of chronic urticaria and angioneurotic edema the drug was effective, relieving the itching and reducing or abolishing the lesions as long as the medication was continued. Of 10 patients with acute urticaria, 8 obtained symptomatic relief, but the medication did not affect the expected duration of the attack. In 14 patients with dermatographism, pyribenzamine controlled the welting and itching, while in 2 cases it failed to have this effect.

Pyribenzamine was given to 20 patients having atopic dermatitis and complaining of marked itching. Included in this group were infants, children and young adults. The itching was decidedly relieved in 16 of these patients, and not infrequently the subsidence of the scratching was reflected in improvement of the lesions. In some of this group only nightly doses were required. Two out of 3 cases of unclassified

dermatitis experienced relief from itching, while 2 patients with a barbiturate rash with great discomfort from itching were entirely relieved. Three patients with pruritus vulvæ of several years duration were maintained symptom-free over a period of 3 months.

Six instances of severe allergic reactions to penicillin, administered orally or parenterally, are included in this series. The manifestations resembled serum sickness and consisted primarily of urticaria and angioneurotic edema, pain and swellings of joints and fever. The skin manifestations were benefited by the use of pyribenzamine, although the joint symptoms were more resistant to therapy. In each case the symptoms returned when the drug was discontinued, and the course and duration of the disease were of the usual character.

Ninety-five patients with typical histories and findings of allergic rhinitis were treated with this medication. In 57 there resulted undoubted improvement; in 38 there was no benefit that could be attributed to the drug. Out of 254 patients with seasonal hayfever, 210 were symptomatically improved. Out of a total of 70 patients with chronic asthma, 24 showed improvement; the degree of relief, however, was not as marked as is usually obtained with ephedrine or epinephrine.

Three patients with frequently recurring headaches of unidentified (but possibly allergic) etiology were treated with pyribenzamine. One had repeated relief whenever the drug was administered. A patient with gastro-intestinal symptoms, probably of allergic origin, failed to obtain benefit from this drug, while another patient with distinct gastro-intestinal allergy was benefited. Our therapeutic results in most of the allergic manifestations are comparable to those obtained by Arbesman and his associates.¹

Side Reactions. The undesirable symptoms from the use of 50 to 100 mg. doses of pyribenzamine were rarely of sufficient severity to interfere with its use. Perhaps the most frequent symptoms could be attributed to sedation or to cerebral stimu-

lation, and consisted of slight drowsiness, vertigo, trembling, nervousness or faintness. Such reactions occurred in about 25 % of a total of over 300 persons to whom this drug was administered. Insomnia was noted in several, dryness of the mouth or nose in a few, and headache in 4. Several mentioned gastric discomfort, usually of a mild character. Two patients complained of burning on urination, 2 of diarrhea and 2 of tightness in the chest.

Thus far no serious toxic effects have been observed in any case in which the

of urticaria and angioneurotic edema and in itching of atopic dermatitis and other dermatoses.

2. About 59 % of patients with chronic allergic rhinitis and 82 % of seasonal hay fever have obtained symptomatic relief of their rhinitis, sneezing or nasal blocking. Twenty-four out of 70 patients with asthma obtained moderate relief. The drug is also of value in the serum-sickness type of allergic reaction.

3. The toxic effects of this drug are rather mild, but fairly frequent, consisting

TABLE 1.—THERAPEUTIC EFFECTS OF PYRIBENZAMINE

	Cases Treated	Improved	Unimproved
Urticaria, chronic	27	21	6
Urticaria, acute	10	8	2
Atopic dermatitis	20	16	4
Dermographism	16	14	2
Dermatitis, unclassified	3	2	1
Penicillin reactions	6	6	0
Sulfonamide reactions	2	2	0
Barbiturate dermatitis	2	2	0
Pruritus vulvæ	3	3	0
Chronic allergic rhinitis	85	50	35
Seasonal hayfever	254	210	44
Asthma	70	24	46
Chronic headache	3	1	2
Gastro-intestinal allergy	2	1	1

drug has been used for a period of weeks. Nevertheless, blood studies and other clinical observations will need to be continued for a long period before the question of chronic toxicity can be fully evaluated.

Summary. 1. A new antihistaminic substance, pyridil - n'-benzyl - n - dimethylethylene-diamine hydrochloride (pyribenzamine), is capable of producing symptomatic relief in a high percentage of cases

primarily of drowsiness, dizziness, nervousness, insomnia, gastric irritation and dryness of the nose and mouth.

4. Pyribenzamine and similar drugs at best can only be palliative. They do not cure the allergic condition. There still remains the necessity for the specific management of the allergic patient by avoidance of exposure to the antigen or by increasing the tolerance to the latter by specific means.

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THE PATHOLOGY OF EXPERIMENTAL FROSTBITE*†

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THIS study is an attempt to correlate the morphologic aspects of the reactions of tissues to cold with modern physiologic concepts of the effects of low temperatures. Several interpretations of the pathogenesis of frostbite and trench foot have been advanced, but recent anatomic investigations^{1,2} have shown that the fundamental lesions are vascular. Since it has been demonstrated³ that heparin prevents the development of gangrene after exposure to cold, an observation which supports the view that thrombosis is important in the pathogenesis of the lesions, it seemed worthwhile to compare histologically the tissues of animals which had received heparin and were subjected to freezing with those of animals similarly exposed without receiving the drug.

Methods. The 40 rabbits employed weighed between 2200 and 3200 gm. Each animal was anesthetized with sodium pentothal, and 1 hind leg, which had been clipped, depilated with barium sulfide cream and covered by a rubber condom, was immersed up to the knee in 95% ethyl alcohol for 30 minutes. The alcohol had been chilled by solid carbon dioxide and was kept at a temperature of -30° C. by immersion of the container in the same material. After exposure the leg was cleaned in an aqueous solution of merthiolate and kept covered by dry sterile dressings during the 2 days following; sulfathiazole cream or dressings soaked in penicillin were applied subsequently.

Half of the animals received heparin; 50 mg. of the drug was given intravenously immediately after exposure, and the dose was repeated every 12 hours for 6 days. The clotting time of the blood was estimated by the Lee-White method every day immediately before the injection of heparin. In most instances it was prolonged to at least 30 minutes. Rabbits which received heparin but were not exposed to cold served as controls.

Representative animals were killed by the intravenous administration of 4 cc. of sodium pentothal 2, 3, 6, 7 and 9 days after freezing, and the exposed legs were fixed in a solution of formaldehyde. Blocks were embedded in paraffin, and sections, cut at 7 microns, were stained with hematoxylin and eosin; and Weigert's fibrin stain, the Brown and Brenn stain for bacteria and the Giemsa stain were also employed. Frozen sections were stained for fat with Oil Red O. The posterior tibial nerve and its plantar branches were dissected out as far as the bases of the toes. Frozen sections of nerve were stained for fat and for myelin (Spielmeyer method). The Bodian method was used to demonstrate axis cylinders in paraffin sections of nerve.

Physiologic Observations. The legs remained cold and white for 30 to 60 minutes after removal from the alcohol and then became red, hot and edematous; redness persisted for about 2 days and swelling for 4 or 5 days. Vesicles appeared on the toe pads, and the fluid in the blisters later coagulated. Some animals had subcutaneous hemorrhages, particularly those

* Part of this work was carried out under contract between the New York Medical College and the Office of Scientific Research and Development and later the Office of the Surgeon-General of the Army.

† Read before the American Society for Experimental Pathology at the meeting of the Federation of American Societies for Experimental Biology, Atlantic City, N. J., March 13, 1946. (Abstr., Fed. Proc., 5, 220, 1946).

which had not received heparin; a few small ulcers appeared at sites traumatized by clipping.

The exposed legs of all untreated rabbits began to show necrosis 4 days after exposure, and gangrene was complete within 10 days (Figs. 1 and 2). No rabbit which had received heparin and consistently shown a clotting time of 30 minutes or longer gave evidence of gangrene (67% of the treated animals) (Figs. 2 and 3), although the legs remained edematous and pink for about a week after exposure. The clotting time for 33% of the treated animals was occasionally less than 30 minutes; gangrene developed in the legs of about half of this group (14% of the treated animals).

All of the animals gave evidence of motor paralysis and sensory disturbance immediately after exposure. The damaged legs dragged, and the reaction to pinprick was abnormally slow or absent. The rabbits which had received heparin showed these abnormalities for 3 or 4 weeks; those which had not been treated exhibited them until gangrene complicated the picture.

The results of special studies of the capillaries will be reported in detail elsewhere,⁴ but the observations can be summarized as follows: As the tissues were cooled, the vessels dilated and the flow of blood became rapid. The blood flow became sluggish when the freezing point was neared, and clumping of the red cells occurred although there was no loss of plasma from the vessels and capillary permeability to fluorescein was not increased. When the temperature of the tissues was lowest, vascular contraction caused cessation of blood flow. After thawing of the tissues, relaxation of the vessels and reestablishment of blood flow, capillary permeability to fluorescein was increased.

Morphologic Observations. UNTREATED RABBITS. Two days after exposure, necrosis was evident in the legs of the animals which did not receive heparin, and the zones of gangrene were sharply demarcated after 6 days (Fig. 4). The

necrotic areas were bordered by regions of diffuse cellulitis and were sometimes delimited by an inflammatory wall. Gram positive cocci were present in both deep and superficial tissues. Granular precipitated protein material, occasional strands of fibrin and moderate numbers of red cells and leukocytes were scattered throughout the diffusely edematous tissues, even at a considerable distance from necrotic areas.

The skin showed vesiculation (Fig. 5), hemorrhagic necrosis and hemorrhage and cellular infiltration about the appendages. No degeneration of muscle was seen 2 days after exposure, although the fibrous septa were edematous and contained necrotic leukocytes. After 6 days typical circumscribed infarcts were noted in the muscle (Fig. 4), and necrotic plugged vessels could be discerned amidst the dead fibers. Productive inflammatory reactions involved the synovial surfaces. No alteration was observed in fat 2 days after exposure, but little adipose tissue was present in the injured portions of the legs; after 6 days necrosis of fat and lipogranulomatous reactions were seen. Proliferation of fixed mesenchymal elements and fibrosis were evident.

Throughout the tissues vascular changes were observed. All the small vessels were dilated, rounded and packed with erythrocytes (Fig. 6). The vascular channels were so prominent that the tissues looked as if they had been injected for purposes of demonstration (Fig. 7). The individual red cells within the clumps could be discerned as separate elements 2 days after exposure. A few small hyaline masses, composed of platelets and a little fibrin, were present in the lumens of occasional vessels, and similar material was plastered along the lining of others (Fig. 8). The vascular walls had a hyalinized homogenized appearance but did not exhibit true fibrinoid necrosis. Red cells had entered the walls and adventitial sheaths, and sometimes the extravasated erythrocytes formed columns between the elastic lamellae (Fig. 9). A few perivascular collections of inflammatory cells were noted. Frag-

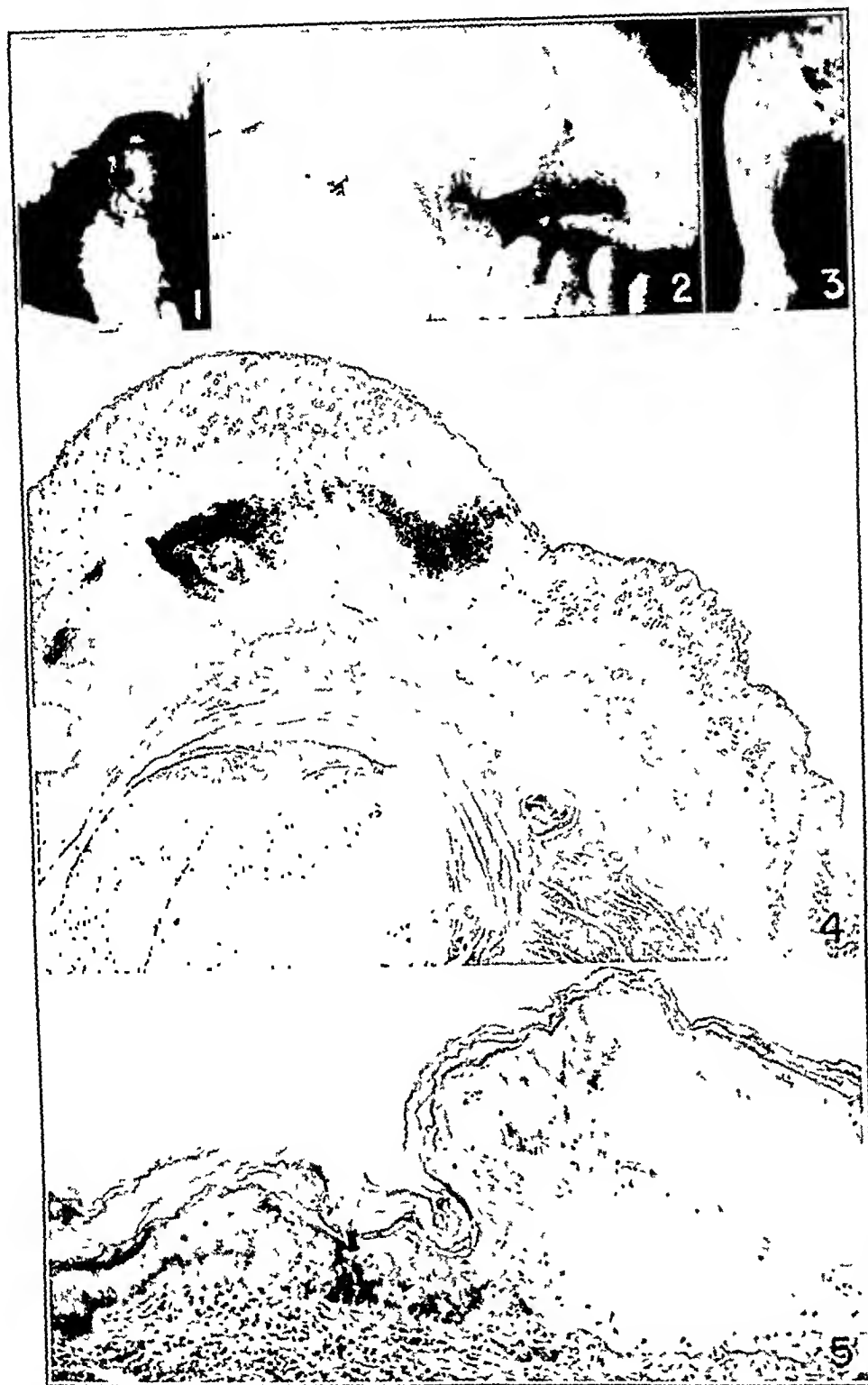


PLATE 1

FIG. 1.—Gangrene of leg of rabbit not treated with heparin, 6 days after exposure to freezing.

FIG. 2.—Gangrenous leg of untreated rabbit (right) and normal leg of rabbit treated with heparin (left), 10 days after exposure of both animals.

FIG. 3.—Normal leg of rabbit treated with heparin, 6 days after exposure.

FIG. 4.—Necrosis of skin and subcutaneous tissue and infarction of muscle. (Untreated rabbit; 6 days after exposure.) Hematoxylin and eosin stain. $\times 10$.

FIG. 5.—Epidermal vesicle. (Treated rabbit; 2 days after exposure.) Hematoxylin and eosin stain. $\times 160$.

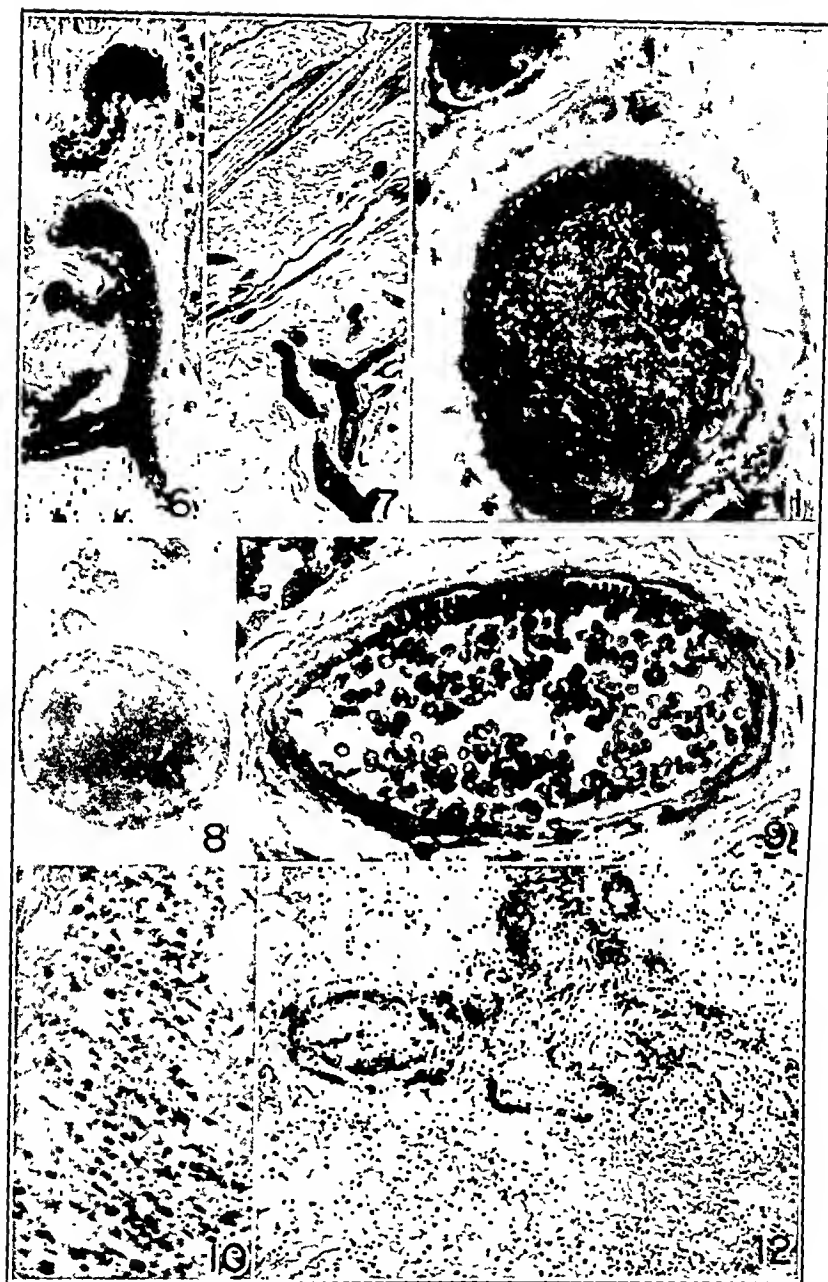


PLATE 2

FIG. 6.—Small vessels packed with red cells. (Untreated rabbit; 2 days after exposure.) Hematoxylin and eosin stain. $\times 315$.

FIG. 7.—Dilatation and engorgement of subcutaneous vascular plexus and edema and cellular infiltration of connective tissues. (Untreated rabbit; 6 days after exposure.) Hematoxylin and eosin stain. $\times 210$.

FIG. 8.—Agglutinated mass of red cells and parietal layer of hyaline material in vessel. (Untreated rabbit; 6 days after exposure.) Hematoxylin and eosin stain. $\times 210$.

FIG. 9.—Columns of erythrocytes penetrating wall of vessel. (Untreated rabbit; 1 hour after exposure.) Hematoxylin and eosin stain. $\times 550$.

FIG. 10.—Mural angitis, migrating leukocytes and cellular debris. (Untreated rabbit; 2 days after exposure.) Hematoxylin and eosin stain. $\times 450$.

FIG. 11.—Thrombus in vessel. (Untreated rabbit; 6 days after exposure.) Hematoxylin and eosin stain. $\times 450$.

FIG. 12.—Thrombus in vessel and cellular infiltration of vessel walls and edematous connective tissue. (Untreated rabbit; 6 days after exposure.) Hematoxylin and eosin stain. $\times 130$.

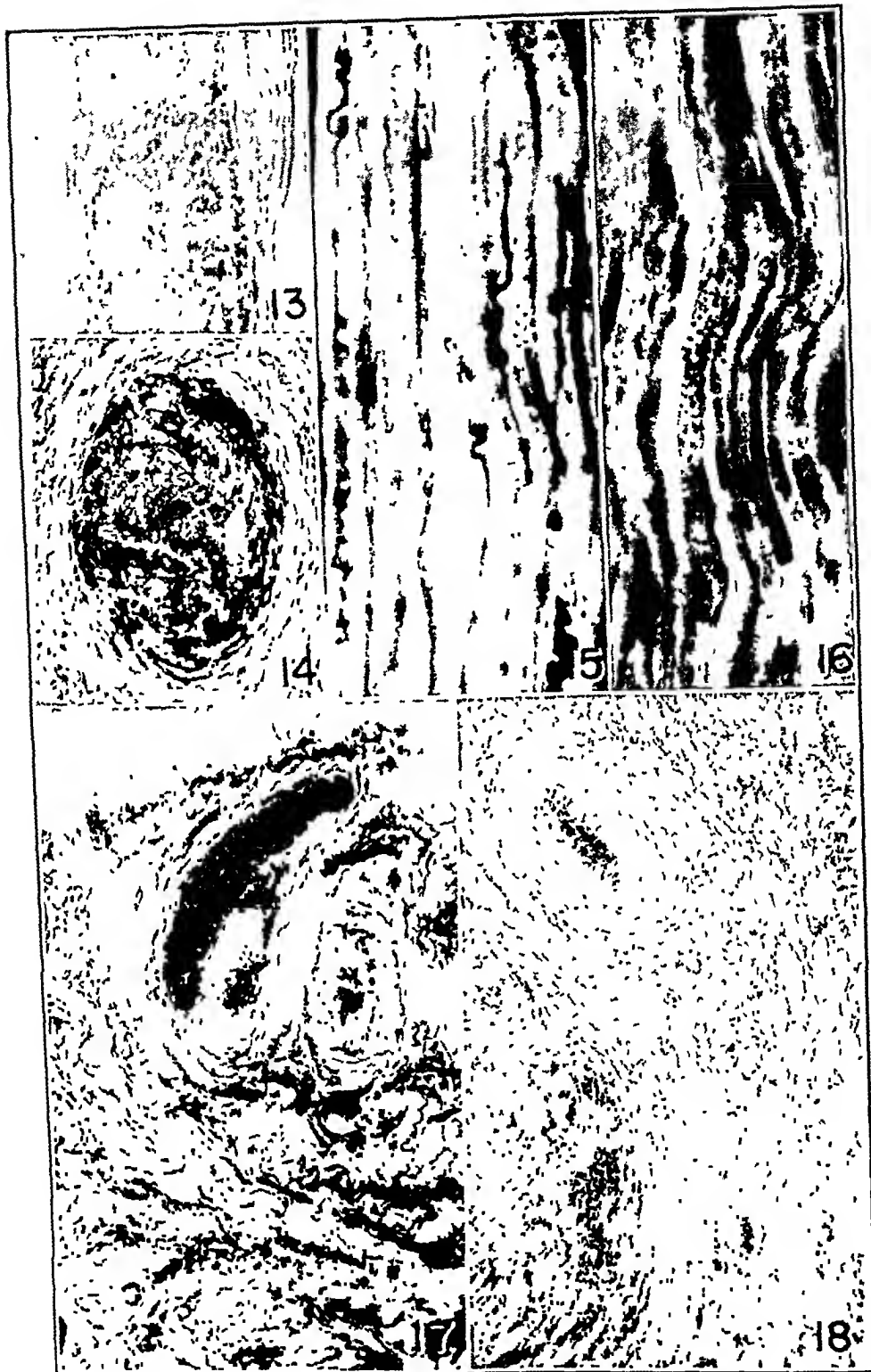


PLATE 3

FIG. 13.—Fused clump of red cells undergoing hemolysis. (Untreated rabbit; 6 days after exposure.) Hematoxylin and eosin stain. $\times 210$.

FIG. 14.—Fibrinous thrombus in vessel near area of gangrene. (Untreated rabbit; 6 days after exposure.) Phosphotungstic acid hematoxylin stain. $\times 185$.

FIG. 15.—Necrotic distorted axis cylinders in nerve trunk. (Untreated rabbit; 6 days after exposure.) Bielschowsky stain. $\times 450$.

FIG. 16.—Degeneration of myelin sheaths. (Untreated rabbit; 6 days after exposure.) Spielmeyer stain. $\times 450$.

FIG. 17.—Normal vessels and normal separation of cells and plasma. (Rabbit treated with heparin; 7 days after exposure.) Hematoxylin and eosin stain. $\times 60$.

FIG. 18.—Normal vessels and surrounding hemorrhage. (Treated rabbit; 2 days after exposure.) Hematoxylin and eosin stain. $\times 50$.

mented mural elements and infiltrating leukocytes were seen in the walls of some vessels (Fig. 10).

Six days after exposure the intraluminal plugs and the parietal layers of hyaline material were prominent (Figs. 11 and 12). The vessels were still jammed with red cells, but in some places the clumps had fused so that individual erythrocytes were no longer discernible. Some homogenized masses of red cells (Fig. 13) had a greenish discoloration, which probably resulted from breakdown of hemoglobin. Diffuse staining by hemolyzed blood was also noted in gangrenous areas. In regions of necrosis plugged arteries and veins could be seen; these channels and those at the edges of the gangrenous zones contained more fibrin (Fig. 14) than vessels elsewhere. Even in viable tissues the vascular walls were more necrotic and inflamed than they had been 2 days after exposure.

Neural changes were observed in areas of edema, hemorrhage, necrosis and cellulitis; intrinsic changes were not noted in the nerves in other regions. The edematous perineural tissues contained inflammatory cells. The capillaries supplying the nerves were sometimes dilated and packed tightly with red cells (described as "plugs of agglutinated corpuscles" by Denny-Brown⁵). Disintegration of myelin sheaths (Fig. 16) preceded breakup of the axis cylinders. The myelin became granular and broke into clumps, but, surprisingly, no neutral fat or phagocytes were noticed. The segmented nerve fibers lay in twisted coils (Fig. 15). In some places the entire nerve trunk was necrotic.

TREATED RABBITS. An occasional ulcer or small area of necrosis was encountered in tissues from the treated rabbits, but for the most part only edema, hemorrhage (Fig. 18) and slight cellular infiltration were noted. The legs of the few treated animals which exhibited gangrene were not examined microscopically. There was pronounced fibrosis in a region of inflammation in 1 specimen. In the tissues of animals killed 6 days after exposure the perivascular and perineural fixed mes-

enchymal elements showed activation and proliferation; cellular proliferation, edema and hemorrhage were also seen in the tissues of rabbits which had received heparin but had not been exposed to cold.

The epidermis showed focal vesiculation and cleavage at the basal layer; in 1 necrotic crust bacteria were visible. There was a suggestion of hyaline change in some muscle fibers 2 days after exposure, but after 6 days the muscle was entirely normal. Mucinous change was noted in the adipose tissue, and adjacent to some nerves were patches of fat necrosis.

The vessels and their contents appeared normal (Figs. 17 and 18) except within the rare foci of necrosis; there, as in the tissues of the rabbits which had not received heparin, erythrocytic plugs were present in dilated vessels. There was no hyperemia, and little fibrin was encountered in the vessels and the interstitial tissues.

Most of the nerves were normal, but some showed hemorrhage and leukocytic infiltration, and there was an occasional perineural inflammatory reaction. Degeneration of myelin or axis cylinders was not noted.

Comment. The legs of rabbits which have been subjected to freezing initially show vasoconstriction; after thawing there are characteristic vascular engorgement and conglutination of red cells. Agglutinative thrombi, poor in fibrin, form and ischemic gangrene follows. Our observations confirm those of Essex and Quintanilla,⁶ who found that heparin did not prevent the early clumping of red cells within the vessels. Heparin apparently does prevent the development of true agglutinative thrombi from the clumped erythrocytes by interfering in some way with the adhesiveness of the packed red cells, and consequently vascular lesions do not appear and gangrene does not ensue. Whether the conglutination bears a relation to cold hemagglutinins⁷ has not been worked out. This phenomenon may be compared with the clumping which has

been observed in malarial blood and with the "sludging" which has been described in traumatic shock.⁸

No changes in nerve or muscle attributable to cold directly, such as those described by Blackwood and Russell,⁹ were noted. In the tissues of the untreated rabbits degeneration of myelin sheaths and axis cylinders and unequivocal hyaline alteration of muscle fibers were present only where there was obvious damage from ischemia. The treated animals showed no significant abnormalities of neural or muscular tissues. It is not clear why changes similar to those produced by Denny-Brown and co-workers⁵ by

freezing and cooling the exposed sciatic nerves of cats were not encountered. It is possible that artificially isolated nerves react differently than do nerves occupying their normal positions. The suggestion that cold has a direct specific action on myelin and fat, first suggested by one of the writers,¹ is further discussed in the paper by the Denny-Brown group.

Summary. The fundamental lesions of frostbite experimentally produced in rabbits are vascular. The formation of agglutinative erythrocytic thrombi leads to vascular occlusion and ischemic gangrene. Heparin prevents the development of both thrombosis and gangrene.

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USE OF POSTERIOR PITUITARY EXTRACT (PITUITRIN) TO MEASURE RENAL FUNCTION

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ALTHOUGH numerous renal function tests have been described, there is still a great need for a simple and dependable test which is adaptable to office practice and allows rapid evaluation of the concentrating power of the kidneys. Recently the use of a concentration test based on the antidiuretic action of posterior pituitary extract (p Pituitrin) has been studied by several investigators.^{3,4,5,6,7,8} Some of these investigators^{4,5,8} believe that the test is accurate enough to be substituted for the fluid restriction tests, while others⁷ have noted wide variations between modifications of the pituitrin test and the Addis concentration test. Schneeberg and his co-workers,³ and Sodeman and Engelhardt^{4,5} have shown that water induced diuresis does not interfere with the pituitrin test, and others^{4,5,8} have found that the test gives a true indication of renal function in patients with congestive heart failure.

We have compared the pituitrin test with a fluid restriction test in a series of patients with and without impaired renal function and in a group of patients with congestive heart failure, both before and after compensation. In addition, the effect of the patient's state of hydration on both tests has been studied.

Material. A total of 67 patients whose ages ranged from 12 to 96 years were studied at the Forsyth County Hospital (a home for the aged and infirm) and the North Carolina Baptist Hospital (a general hospital). These patients were divided into 5 groups: (1) a control group of 14 patients without hypertension or evidence of renal disease; (2) 11 patients with hypertension who showed no evidence of renal disease;

(3) 27 patients with impaired kidney function; (4) 10 patients with congestive heart failure; and (5) 5 patients without evidence of kidney disease in whom the effect of the state of hydration was studied.

The first 3 groups were made up entirely of patients from the Forsyth County Hospital, who were classified by the following method: after a routine history, physical examination, urinalysis, and blood examination, the 2 urinary concentration tests were performed. Patients whose urine showed a specific gravity above 1.020 on any sample, whose blood pressure was normal, and who had no evidence of any disease of which renal inadequacy might be a part, were placed in the control group (Table 1). If the blood pressure was elevated and the maximum specific gravity of the urine was above 1.020, a phenolsulfonphthalein excretion test and non-protein nitrogen determination were made. If these were within the normal range, the patients were placed in the 2nd group (Table 2). The 3rd group consisted of patients with definite evidence of impaired renal function; the additional studies done on these patients are shown in Table 3.

The 4th group was made up of 6 patients from the North Carolina Baptist Hospital and 4 from the Forsyth County Hospital, all of whom had edema due to congestive heart failure when the first tests were done. The tests were repeated after the failure had been compensated and the edema had disappeared (Table 4). Five patients from the North Carolina Baptist Hospital made up the 5th group. These patients had no evidence of kidney disease, and were studied solely to determine the effect of states of relative hydration and dehydration upon the 2 tests (Table 5).

Method. In the fluid restriction test no fluids were allowed after 5 P.M. All urine

voided during the night was discarded, and specimens were collected at 7, 8 and 9 A.M. Only the highest specific gravity is recorded in the tables.

The method described by Wall⁸ for the pituitrin test was used. The patients received no special preparation, and the tests were done at various times of the day. No food or fluid was allowed during the 2 hour test period. The bladder was emptied just prior to the test, and the urine was discarded. One cc. of pituitrin containing 10 U.S.P. units was then injected subcutaneously. Urine was collected 1 and 2 hours after the injection, and the higher specific gravity was recorded. The blood pressure was taken frequently during and after the test.

All determinations of specific gravity were made at the same temperature in a calibrated 7 cc. urinometer. None of the specimens contained sugar, and corrections were made for the albumin content.² In no case was there sufficient albuminuria to raise the specific gravity significantly.

Wall,⁸ from incomplete studies on patients with heart failure, suggested that the pituitrin test is more reliable than fluid restriction tests in patients with severe edema; other workers⁵ have confirmed this idea. In order to evaluate further the effect of edema, both tests were performed in a group of 10 patients with congestive heart failure and were repeated after compensation was complete (Table 4).

It has been generally assumed⁸ that preparation of the patient is not necessary for the use of the pituitrin test, and that the state of hydration does not appreciably affect the results of the test. In order to evaluate further the hydration factor we studied separately 5 patients who had no evidence of renal disease (Table 5). Both tests were performed twice (72 hours apart) and were preceded once by hydration of the patient (2000 cc. of water the evening before and 200 cc. of water every 30 minutes for 4 hours prior to the test) and once by dehydration (no fluids taken for 15 hours prior to the test). The order in which the

tests were performed was varied from patient to patient.

Results. The maximum specific gravities obtained by both tests are recorded in the tables. Excluding the patients with cardiac decompensation and the group studied for the effect of hydration and dehydration, it was found that the fluid restriction test gave a higher specific gravity in 21 (40%) of the cases. The posterior pituitary test gave a higher value in 20 (39%) of the patients, and in 11 (21%) the maximum values obtained by the 2 tests were the same. The greatest variation between the 2 tests in any case was 0.005, and the average variation was 0.0015.

If a specific gravity below 1.020 is taken as an indication of impaired renal function, and the 52 patients in the first 3 groups are classified according to this criterion, it is seen that in 4 cases (marked with an asterisk) the 2 tests failed to agree on the patient's classification. Three of these 4 patients were in the group with renal disease.

The results shown in Tables 1, 2 and 3 were analyzed by determining whether the mean of the differences between the 2 tests is significantly different from zero.*

In the 10 patients tested during congestive heart failure and again after compensation (Table 4) the pituitrin test gave very nearly the same values on both occasions, while the specific gravities obtained by the fluid restriction test were much lower during edema in 70% of the patients. One of the most valuable uses of the pituitrin test will be to determine the status of a patient's renal function during congestive heart failure.

In the 5 patients tested following hydration and dehydration (Table 5), the variations in the maximum specific gravities

* In the control group (Table 1) the calculated value for t is 1.640, while the value found in the table is 2.160. The interpretation of this finding is that the mean of the differences between the 2 tests does not differ significantly from zero. In the group with hypertension without demonstrated renal disease (Table 2), the calculated value for t is 1.024, while the value given in the table is 2.228. The interpretation is the same as for Group 1. In the group of patients with impaired renal function (Table 3) the calculated value for t is 2.333, while the value given in the table is 2.056. Thus, in this group the difference is significantly different from zero.

TABLE 1.—MAXIMUM SPECIFIC GRAVITIES OBSERVED IN PATIENTS WITHOUT HYPERTENSION OR EVIDENCE OF RENAL DISEASE (CONTROL GROUP)

Case No.	Age	Blood pressure	Fluid restriction test	Pituitrin test
1	22	118/80	1.028	1.027
2	36	100/60	1.025	1.023
3	12	110/64	1.025	1.022
4	77	138/88	1.023	1.024
5	24	116/68	1.026	1.027
6	59	136/80	1.028	1.025
7*	60	142/80	1.019	1.023
8	53	130/66	1.029	1.027
9	24	124/82	1.027	1.025
10	41	120/82	1.024	1.023
11	34	130/84	1.024	1.022
12	22	124/80	1.026	1.027
13	36	120/80	1.021	1.020
14	21	120/80	1.028	1.029

* Tests disagree as to adequacy of kidney function.

TABLE 2.—MAXIMUM SPECIFIC GRAVITIES OBSERVED IN PATIENTS WITH HYPERTENSION WITHOUT EVIDENCE OF RENAL DISEASE

Case No.	Age	Blood pressure	Fluid restriction test	Pituitrin test
15	80	200/100	1.022	1.023
16	78	220/110	1.021	1.020
17	57	200/124	1.025	1.025
18	56	160/94	1.025	1.021
19	67	236/140	1.025	1.022
20	60	150/98	1.030	1.025
21	55	150/100	1.025	1.025
22	80	150/96	1.023	1.021
23	42	150/110	1.023	1.023
24	68	180/100	1.031	1.030
25	78	176/90	1.021	1.025

TABLE 3.—MAXIMUM SPECIFIC GRAVITIES OBSERVED IN PATIENTS WITH IMPAIRED RENAL FUNCTION

Case No.	Age	Diagnosis	Blood pressure	Fluid restriction test	Pituitrin test	N.P.N. (mg.%)	P.S.P. (2 hr. %)
26		Arteriosclerotic nephritis	160/78	1.017	1.019	42	40
27	43	"	160/100	1.016	1.018	40	
28	74	"	170/100	1.015	1.017	50	
29	65	"	142/88	1.018	1.016		47
30*	63	"	110/70	1.019	1.021	30	50
31	80	"	142/84	1.015	1.017		48
32	47	"	190/130	1.015	1.015	38	42
33	70	"	156/98	1.014	1.013	60	38
34	54	"	180/100	1.013	1.016		38
36	40	"	150/80	1.017	1.017	35	50
36	50	"	160/104	1.020	1.020		
37	68	"	180/100	1.017	1.017		
38	75	"	122/68	1.017	1.017		
39*	90	"	140/80	1.018	1.020		54
40	79	"	180/80	1.015	1.014	52	40
41	64	"	170/92	1.015	1.018	40	
42	68	"	160/86	1.017	1.018		46
43	76	Necrotizing arteriolitis	225/130	1.016	1.018	46	
44*	72	"	200/110	1.020	1.019	34	54
45	44	"	230/134	1.018	1.019	44	
46	20	"	210/150	1.016	1.016	35	44
47	43	Pyelonephritis	148/98	1.018	1.017		45
48	60	Chronic glomerulonephritis	164/98	1.012	1.014	90	31
49	52	"	200/110	1.012	1.013	84	30
50	96	"	180/90	1.013	1.013	76	24
51	68	"	150/90	1.011	1.010	100	27
52	24	"	155/105	1.010	1.010	110	21

* Tests disagree as to the adequacy of kidney function.

obtained by the 4 tests ranged from 0.001 to 0.003, the average being 0.002. The average of the variations in the 2 fluid restriction tests was 0.0018. The variation between the 2 tests using pituitrin was never more than 0.001, although the specific gravities were usually higher after fluid restriction. These findings agree with the general impression that special preparation of the patient for the pituitrin test is not necessary, and that pituitrin will elevated the specific gravity to satisfactory diagnostic levels regardless of the state of hydration.

second injection produced no symptoms. Of the 52 patients in the first group, 20 (39%) had a stool within the 1st hour after injection, but this was not associated with abdominal pain and in no way disturbed the patient's course. There were no significant alterations of blood pressure in any of the patients, the maximum variation being 10 mm. of mercury. The test was performed in 6 patients with known coronary artery disease, and in none was chest pain produced. These patients were given a test dose of 0.5 cc. (5 U.S.P. units), and a period of 6 hours

TABLE 4.—MAXIMUM SPECIFIC GRAVITIES OBSERVED IN PATIENTS WITH CONGESTIVE HEART FAILURE BEFORE AND AFTER COMPENSATION

Case No.	Age	Diagnosis	Blood pressure	With edema		After compensation		N.P.N. (mg.%)	P.S.P. (2 hr. %)
				Pituitrin	Fluid restriction	Pituitrin	Fluid restriction		
53	40	Rheum. heart disease, mitral stenosis	120/85	1.018	1.014	1.018	1.017	38	
54	66	"	140/80	1.029	1.021	1.029	1.030	37	58
55	45	"	145/80	1.029	1.020	1.028	1.028	43	45
56	51	"	130/78	1.027	1.024	1.028	1.027	34	70
57	42	Syph. heart disease, aortic insufficiency	140/60	1.023	1.014	1.022	1.021	38	70
58	64	Hypertensive heart disease	230/150	1.016	1.012	1.017	1.018	58	
59	64	"	180/120	1.017	1.012	1.019	1.017	52	35
60	47	"	200/126	1.019	1.013	1.019	1.020	40	43
61	49	Arterio-sclerotic heart disease	140/80	1.019	1.018	1.019	1.019	40	
62	73	"	150/80	1.020	1.019	1.020	1.021	38	53

TABLE 5.—MAXIMUM SPECIFIC GRAVITIES OBSERVED IN 5 PATIENTS WITHOUT RENAL DISEASE IN WHOM THE STATE OF HYDRATION WAS VARIED

Case No.	Following hydration		Following dehydration	
	Pituitrin	Fluid restriction	Pituitrin	Fluid restriction
63	1.021	1.021	1.020	1.022
64	1.024	1.024	1.024	1.025
65	1.022	1.022	1.023	1.024
66	1.027	1.026	1.028	1.029
67	1.026	1.026	1.027	1.028

SIDE-EFFECTS OF PITUITRIN. There have been no alarming symptoms reported from the use of posterior pituitary extract in doses of 10 U.S.P. units, although some workers⁷ have noted blanching of the skin and abdominal cramps. Three of the patients in this series (6%) complained of cramping abdominal pains soon after the injection, and 2 others (4%) experienced nausea and vomiting. These symptoms did not interfere with the test, however, and did not persist for more than 10 minutes. In the patients on whom the test was performed twice the

was allowed to elapse before the full dose was given. We believe that a test dose should always be used in patients with coronary artery disease, since the drug is known to produce constriction of the coronary arteries, and is potentially dangerous for such individuals. Discussion. The statistical analysis of the first 3 groups indicates clearly that the fluid restriction and pituitrin tests give extremely close agreement of the concentrating power of the kidneys in patients without renal disease, but that they differ significantly in patients with

impaired kidney function. However, the analysis presupposes that the maximum concentration given by the fluid restriction test is a constant figure and will not vary from day to day. Schneeberg and his co-workers³ stated, without giving data, that there is a significant day-to-day variation in the specific gravities obtained by the Fishberg technique. We have not studied this factor in detail, but it has been our impression that there is a daily variation. If this impression is correct, the statistical analysis is not as significant as it would be otherwise.

Although in 4 cases the tests failed to agree as to the adequacy of renal function (if a specific gravity of 1.020 is taken as a criterion), the actual variations in specific gravities in these 4 cases are small (1.020 and 1.019, 1.020 and 1.018, 1.021 and 1.019, 1.023 and 1.019). If one applies the chi square method of analysis, one finds that chi square is 0.308, a figure which indicates that the difference is not significant and could occur by chance. Our findings indicate that pituitrin can be used as a substitute for the fluid restriction test to measure renal function. Since 3 of the 4 instances of significant failure in agreement were in the group of patients with renal disease, it would appear that the test is not as reliable in patients with diseased kidneys as in patients without kidney disease.

We believe that the pituitrin test is a valuable addition to the group of renal function tests. The advantages of the test are numerous. It does not require a prolonged period of fluid restriction, and may be carried out without special preparation of any kind—a very great advantage in the unintelligent or uncoöperative patient. The test is of particular value in office practice, since it is completed in 2 hours and saves the patient the inconvenience of a second trip to the office. The test is also valuable in preoperative cases where it is not feasible to postpone operation for a day or where fluid restriction is contraindicated.^{3,4,5,6,7,8}

Perhaps the greatest advantage of the

test is its reliability in the presence of edema. It is not reliable, however, in patients who have had mercury or xanthines, since these drugs inhibit the anti-diuretic action of the pituitrin.

The disadvantages of the test are few. In a few instances it was difficult to obtain urine specimens, but this difficulty was usually encountered in the fluid restriction tests on the same patients. We believe that it was due to inability of the patient to void voluntarily rather than to inadequate excretion of urine, since specimens were obtained easily by catheterization in the few cases in which it was necessary to resort to this measure. However, the volume of urine obtained during the pituitrin test was frequently so small that a 7 cc. urinometer had to be used.

The pituitrin test is potentially dangerous in patients with angina pectoris and is contraindicated in pregnancy, even in the first trimester, because of the danger of uterine tetany and fetal death. Except in this small group of patients, however, the test can be safely performed whenever it is necessary to measure the concentrating ability of the kidneys.

Summary and Conclusions. 1. In 25 patients without renal disease the fluid restriction test and pituitrin test gave comparable results; but in 27 patients with impaired kidney function there was a statistically significant difference. However, the statistical analysis was of necessity based upon the invalid assumption that the fluid restriction test gives a constant result.

2. In most cases the pituitrin test determined accurately whether or not a given patient should be classified as having impaired renal function. It may be substituted for the fluid restriction test to measure the concentrating ability of the kidneys, although greater variation occurred in patients with the diseased kidney, than in patients without kidney disease.

3. The posterior pituitary test accu-

rately measured the concentrating power of the kidneys in 10 patients with edema, whereas the fluid restriction tests gave an abnormally low specific gravity in these patients. The posterior pituitary gave a value that does not differ significantly from the same test or the fluid restriction test after the patient has compensated.

4. The prevailing state of hydration does not significantly influence the results

obtained with the posterior pituitary test in the 5 patients tested. -

5. The posterior pituitary test requires no special preparation of the patient, is completed in a short period of time, and produces no untoward reactions in the average patient. It is contraindicated in pregnancy, however, and is potentially dangerous in individuals with coronary artery disease.

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THIOURACIL IN THYROTOXICOSIS. RESULTS OF PROLONGED TREATMENT IN 35 CASES

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THE introduction of new compounds which exert an inhibitory effect upon the activity of the thyroid gland presents 2 possible advantages. Such compounds might prove of value either (a) when used over relatively short periods of time as adjuvants to, or substitutes for, iodine in the preparation of the thyrotoxic patient for thyroidectomy; or (b) as substitutes for thyroidectomy and other forms of treatment in the production of a prolonged or permanent remission in the thyrotoxic state. The effects of thiouracil, the most prominent of the new "antithyroid" compounds, have been so extensively studied and described that the usefulness and limitations of this drug as a pre-operative agent are by this time relatively well understood.^{1,2,5} However, evaluation of the ultimate usefulness of thiouracil in the permanent control of thyrotoxicosis must await more prolonged observation of larger numbers of patients followed for long periods of time. The limited number of references^{1,5} in the literature to the results of prolonged therapy with thiouracil is doubtless due chiefly to the fact that this drug has been in general clinical use for somewhat less than 3 years. Additional reports on this phase of the problem are desirable. It is our purpose here to report observations on 35 thyrotoxic patients who have received thiouracil for protracted periods and who have been under observation for intervals varying from 10 to 30 months. Data of chief interest pertaining to our cases are presented in Table 1.

We have divided our patients into the following 3 groups: (1) patients in whom sustained remission has followed the cessation of thiouracil therapy; (2) (a) patients

who have remained in remission on small maintenance doses of thiouracil, but who have relapsed when such maintenance doses were withdrawn, (b) patients who have relapsed when the dosage of thiouracil was reduced, and (c) patients maintained in remission on small doses of thiouracil, without withdrawal of the drug; (3) patients who, despite prolonged therapy, have shown doubtful or unsatisfactory response.

GROUP 1. Only 1 of these 16 patients was a male and all but 3 were less than 50 years of age. The thyrotoxicosis was considered to be mild or moderate in severity in all cases. Only 1 patient presented a nodular goiter; in the others the thyroid enlargement was diffuse, uniform and slight or moderate in degree. None of the patients had received iodine, irradiation, or any other specific therapy directed toward the thyroid for at least 1 month prior to the beginning of thiouracil; and in no instance had a previous thyroidectomy been performed. Two patients presented independent complicating diseases: 1 suffered from essential hypertension, arthritis, a uterine fibroid, and secondary anemia; the other (with a nodular goiter) suffered from hypertension, angina pectoris, and chronic cholecystitis.

The average period of maximum thiouracil dosage (0.6 to 1 gm. daily) was 1.2 months, the shortest period of maximum dosage was 0.5 month, and the longest 2.5 months. The average duration of therapy was 6 months; the shortest period during which the drug was administered was 1 month, and the longest period was 10.25 months. Among the 9 patients who have remained well for

1 year or more following the withdrawal of therapy, the average period of treatment was 5.5 months, the minimum 1 month, and the maximal period 9.5 months. The duration of observation following the withdrawal of therapy is shown in Table 1.

slight exophthalmos or lid retraction. Neither of these signs was aggravated except in 1 patient who showed a slight unilateral increase in exophthalmos, which appeared 2 months after treatment was started, and has persisted throughout 12 months of subsequent observation.

TABLE 1.—DATA PERTAINING TO DIAGNOSIS AND TREATMENT OF 35 THYROTOXIC PATIENTS RECEIVING THIOURACIL

	Group 1	Group 2	Group 3
	Sustained post-therapeutic remissions	Remissions only during therapy	Unsatisfactory response
Number of patients:	16	13	6
Total period of observation:			
6-12 months	3	4	2
12-18 "	4	1	2
18-24 "	1	7	0
24-30 "	8	1	2
Relapses	4*	11	4
Remissions	16	11	0
Age:			
10-19 years	3	0	1
20-29 "	1	7	0
30-39 "	3	3	0
40-49 "	6	0	2
50-59 "	2	3	1
60-69 "	1	0	2
Sex:			
Female	15	10	5
Male	1	3	1
Type of goiter:			
Diffuse	15	8	3
Nodular	1	2	3
Recurrent postoperative	0	3	0
Total therapy (months):			
Average	6	13	17
Minimum	1	6	7
Maximum	10 8	20	26
Follow-up after withdrawal of drug:			
3- 6 months	4		
6-12 "	3		
12-18 "	3		
18-24 "	4		
24- "	2		

* The 4 relapses noted in Group 1 occurred early in our study, the drug being withdrawn too soon in these cases; these patients subsequently responded to resumption of therapy, and ultimately showed sustained remissions.

Four patients in this group relapsed following the first withdrawal of thiouracil, but were promptly controlled again following readministration of the drug. In these cases the drug was withdrawn after 5, 2.25, 1.5 and 1 month respectively, symptoms of relapse became apparent in 1, 2.5, 2 and 0.5 month respectively. No patient in this group showed ocular involvement of a more serious nature than

The criteria for the determination of remission in this group have included complete subjective relief, weight gain, and the return of the basal metabolic rate and heart rate to normal levels. Reduction in size of the thyroid gland was not considered a prerequisite component of a remission. In this group the thyroid definitely decreased in size in 7 patients,

showed no change in 8, and increased in 1 (patient with a nodular goiter).

GROUP 2. (a) Only 1 of these 9 patients was a male, and the majority of the group was less than 40 years of age. The thyrotoxicosis was classified as mild in 2 cases, moderate in 6, and severe in 1. The thyroid enlargement was diffuse in 7 patients (4 slight, 3 moderate) and nodular (postoperative recurrence) in 2 instances. Except for 1 patient who received iodine for 3 weeks immediately prior to treatment, no patient in this group had received therapy directed toward the thyrotoxicosis within at least 2 months prior to the beginning of thiouracil. No patient in this group presented any independent complicating disease.

basal metabolic rate of +30% also received 1000 r units of irradiation to the pituitary. Estrogen, a short course of iodine, and 1 series of irradiation treatments to the thyroid were also given subsequent to her relapse following the withdrawal of thiouracil. After 10 months observation there has been no significant change in her ocular condition. Another patient, a man aged 68, with a slight diffuse goiter and a basal metabolic rate of +65% was given estrogen intermittently in addition to thiouracil. He suffered 2 episodes of exposure keratitis 7 and 14 months after thiouracil was begun. After 21 months of treatment his exophthalmos has increased about 5 mm. in each eye, but the edema and congestion

TABLE 2.—TOXIC REACTIONS ATTRIBUTED TO THIOURACIL IN 5 PATIENTS.

Patient	Duration of therapy prior to 1st episode	Daily dosage at time of 1st episode (gm.)	Lowest total leukocyte count (thous./c.mm.)	Lowest % of neutrophils	No. of episodes	Symptoms
1. M. C.	6 mos.	0.2	2.5	30	2	Pharyngitis
2. V. C.	23 days	0.6	1.2	12	2	Pharyngitis, chills, and fever
3. V. M.	1.5 mos.	0.2	2.8	44	3	Cervical adenopathy and fever
4. A. S.	6 "	1.0	2.8	18	3	None
5. T. C.						
Leukopenia	15 "	0.1	1.8	41	3	Pharyngitis
Rash	3 wks.	0.6	None

The average period of thiouracil therapy in this group was 12.6 months, the minimal period being 5.75 months, and the maximal period 19.5 months. The dosage of thiouracil was irregular, varying from an initial maximal dose of 0.6 to 1 gm. daily to a minimal dose of 0.1 to 0.2 gm. daily. Maintenance of remission did not in any case require a daily dose greater than 0.2 gm. The maximal period of sustained therapy prior to any relapse averaged 5.75 months; the shortest period of therapy prior to a relapse was 1 month, and the longest was 11 months. The approximate average time required for symptoms of relapse to become apparent was 2.7 months, the shortest time being 1 month, and the longest being 5 months. Three patients presented moderately severe signs of ophthalmopathy (edema and congestion of lids and conjunctivæ, with slight superficial corneal erosion in 1 case). One of these patients, a woman aged 38, with a slight diffuse goiter and an initial

of the lids and conjunctivæ have decreased. The third patient was a Negro woman, aged 34, with a nodular, postoperative regrowth of the thyroid and moderately severe thyrotoxicosis. Her ocular signs included exophthalmos, edema of the lids, and enlargement of the lacrimal glands. After 17 months of intermittent thiouracil therapy the exophthalmos had increased by 4 mm. in each eye. The condition of the lids and lacrimal glands was unchanged but the cornea remained intact and visual acuity had not changed. Thiouracil was then withdrawn because of the increase in exophthalmos. One year after withdrawal the exophthalmos had increased further by 1 mm. in each eye.

(b) The 2 patients in this group were a Negro male, aged 28, with a nodular goiter; and a white female, aged 31, with a nodular thyroid regrowth associated with chronic persistent thyrotoxicosis following a partial thyroidectomy 8 years previously. The first patient relapsed

within 1 month after having received 0.6 to 0.4 gm. of thiouracil daily for 1.75 months and 0.2 to 0.1 gm. daily for 1.25 months. He relapsed a second time 4 months later, 1 month after the daily dose had again been reduced to 0.1 gm. The dosage was again reduced to 0.1 gm. daily after 3 months, and this time he remained in remission on 0.1 gm. daily for 3 months, when therapy was omitted. He did not return for examination for 5 months at which time he had again relapsed, although his nodular goiter was definitely smaller than before treatment was begun.

The second patient was under treatment for 19 months. During this time she relapsed twice when thiouracil was withdrawn for 1 month or less. She also relapsed 3 times when the daily dose was reduced to 0.1 gm., symptoms recurring once after 1 month and twice after 2 months³ reduction of dosage. During the entire period of therapy her nodular thyroid regrowth increased slowly in size, and her exophthalmos increased slightly. Thiouracil was finally abandoned when recurrent leukopenia appeared after 17 months therapy, and subtotal thyroidectomy was performed following iodination.

(c) These 2 patients remained in prolonged remission on daily maintenance doses of thiouracil not exceeding 0.2 gm. The first patient was a woman, aged 69, with a nodular goiter, diabetes mellitus, moderate hypertension, and mild symptoms of congestive heart failure, with an initial basal metabolic rate of +46%. She received 0.4 to 0.8 gm. of thiouracil daily for 5 months. For the next 6 months she was kept in remission on a daily dose varying from 0.3 to 0.05 gm. During this time her goiter increased in size despite the intermittent use of iodine and desiccated thyroid. Subtotal thyroidectomy was performed because of increasing pressure symptoms.

The second patient was a male, aged 22, with an initial basal metabolic rate of +59%, and a firm, diffuse, moderate thyroid enlargement. He received a

maximal daily dose of 0.6 gm. for 2.75 months, 0.2 to 0.3 gm. for 4 months, and for 4 months has been maintained in remission on 0.1 gm. daily. His goiter has decreased markedly in size and firmness.

Among the 13 patients in Group 2 the thyroid enlargement showed no change in 3, increased in size in 3, and decreased in 7. Among the latter were 2 of the 5 nodular goiters. Ocular manifestations were unchanged in 9 cases, increased in 3, and decreased in 1 instance.

GROUP 3. The 6 patients in this group have failed to show clear-cut response to thiouracil, despite periods of treatment varying from 7 to 15 months. The average period of treatment was 11.5 months. Only 1 of these patients was a male. Five of the patients were above 44 years of age. The outstanding feature in this group was the presence of complicating diseases in 4 cases. None of the patients in this group received significant therapy directed toward the thyroid prior to the beginning of thiouracil administration. Only 1 patient showed ocular signs (slight stare and exophthalmos); these were not affected by treatment.

Brief protocols of these cases are given below:

1. C. De L., a white woman, aged 44, with acromegaly, slight diffuse goiter, hypertension, and slowly progressive cardiac failure. The initial basal metabolic rate was +64%. Despite the almost continuous administration of 0.2 to 0.6 gm. thiouracil daily for 15 months, the basal metabolic rate did not show a sustained reduction, although the slight thyroid enlargement ultimately decreased in size, congestive heart failure gradually progressed, causing death after 18 months of observation. Differential evaluation of the respective influence of the pituitary disease, the hypertension, and the heart failure upon her basal metabolic rate was difficult. However, it was believed that thyrotoxicosis, possibly secondary to hyperpituitarism, was present and probably contributed in some degree to her cardiac failure.

2. T. W., a white woman aged 61, with moderate hypertension, myocardial enlargement and degeneration, a nodular goiter,

and an initial basal metabolic rate of +73%. Despite a decline in the basal metabolic rate and gain in weight, she has not shown a sustained or complete remission after 1 year of thiouracil therapy, with daily dosage of 0.4 to 0.6 gm., and her goiter has increased somewhat in size. The influence of the hypertension has been difficult to evaluate.

3. A. B., a white woman, aged 64, with nodular goiter, diabetes mellitus, weakness of the right arm apparently associated with a cerebral lesion of uncertain nature, and an initial basal metabolic rate of +37%. Seven months of thiouracil therapy (0.4 to 0.6 gm. daily) failed to produce a complete remission, the lowest basal metabolic rate during this time being +20%. The goiter did not change appreciably in size. The patient was finally subjected to thyroidectomy, after the addition of iodine, with a satisfactory result.

4. V. M., a white girl, aged 13, had rheumatic mitral valvular disease, idiopathic epilepsy, diabetes mellitus, and a slight diffuse goiter, with an initial basal metabolic rate of +27%. Thiouracil was withdrawn after 22 months of occasionally interrupted therapy, because of recurrent leukopenia. During this time the patient had gained 44 pounds and had grown 1 inch, but the diabetes had not been ameliorated. Her thyrotoxic status had been difficult to evaluate because of emotional instability and other factors. However, at the time of final withdrawal of thiouracil it was felt that a sustained remission had not been produced although her basal metabolic rate was +1%. Three months after thiouracil was stopped her basal metabolic rate was -2% but she still showed tachycardia and emotional instability.* This patient has been reported in a previous communication.⁴

5. M. K., a white woman, aged 57, presented a slight diffuse thyroid enlargement, with an initial basal metabolic rate of +38% and evidence of slight cardiac insufficiency. After 10 months of occasionally interrupted therapy she showed no significant improvement. Thiouracil was then discontinued and 3 months later her status was essentially unchanged. This patient had been rather uncoöperative and irregular in her visits to the clinic, and her failure to respond may

in part be due to this irregularity rather than to inadequacy of thiouracil therapy *per se*.

6. A. S., a Negro male, aged 49, presented evidence of severe thyrotoxicosis with a nodular goiter, intermittent auricular fibrillation, edema of the legs, marked weight loss, and an initial basal metabolic rate of +62%. He received 0.6 to 1 gm. of thiouracil daily, with 1 brief intermission, for 8 months; an intermediate dose (0.3 to 0.4 gm. daily) for 3 months; and a maintenance dose (0.1 to 0.2 gm. daily) for 0.5 months. His therapy was interrupted on 3 occasions for periods varying from 2 to 4 months because his work prevented regular visits to the clinic, and because the appearance of leukopenia twice necessitated the withdrawal of therapy. After 21 months of observation his goiter was smaller and he was generally improved, but still moderately thyrotoxic. Because his work prevented regular clinic visits, and because leukopenia had again recurred, thiouracil was abandoned and thyroidectomy was advised. As in Case 5, unavoidable interruptions of therapy may have been partially responsible for our ultimate failure to produce a remission.

TOXIC REACTIONS TO THIOURACIL. The reactions were limited to leukopenia and maculo-papular dermatosis, the latter appearing in a patient in whom leukopenia also later occurred. Five patients showed a fall in total leukocyte count below 4000 per c.mm. on 1 or more occasions. One of these (previously reported⁴) developed severe leukopenia (1250 leukocytes with 12% neutrophils), with chills, fever and pharyngitis, after 23 days of treatment (0.6 gm. daily). Thiouracil was subsequently readministered after 1 month of interruption without further toxic effect; this patient has been in a sustained remission for 22 months since final cessation of therapy. None of the other patients who developed leukopenia showed the usual clinical picture accompanying severe granulopenia.

Factors pertaining to the leukopenic reactions are shown in Table 1. It should

* In thyrotoxic children and adolescents, periods of discrepancy between the basal metabolic rate and other manifestations of the disease are frequently observed during and after various types of therapy ("dispersion phenomenon").²

be noted that Patient A. S. showed leukopenia on various occasions when he had received no thiouracil for several months. As William *et al.*⁶ have pointed out, leukopenia occasionally accompanies untreated thyrotoxicosis, a fact which may render interpretation of leukocyte counts made during thiouracil therapy somewhat difficult. In the 1 patient who developed skin lesions, the eruption appeared after 3 weeks of treatment, but soon disappeared despite continuation of thiouracil. A similar eruption recurred after 19 months of intermittent treatment, coincidentally with the reappearance of leukopenia. The incidence of toxic reactions in our cases, selected because of prolonged therapy, does not necessarily reflect the general incidence of such reactions.

Comment. Only tentative conclusions can be drawn from our experience, because of the small number of patients followed and the relatively short period of observation. However, 45.7% of our 35 patients have shown sustained remissions for periods varying from 3 to 29 months following cessation of thiouracil therapy; 25.7% have remained well for 1 year or more. An examination of the data on patients showing sustained remission following cessation of treatment shows that the best results appeared in those with slight to moderate diffuse thyroid enlargement, thyrotoxicosis of mild to moderate severity and without independent complicating diseases or severe ocular signs. In short, these patients were the type who might have been treated by irradiation or other conservative measures with reasonable expectation of ultimate success. They likewise conform to the type in which spontaneous remissions sometimes occur. Only 2 of the 35 patients were considered severely toxic. One of these is well controlled on small maintenance doses, but has twice relapsed when the drug was withdrawn; the other (Case 6, Group 3) was considered to have responded unsatisfactorily and thyroidectomy was recommended. None of the patients in Group 1 has shown evidence of real or sustained hypothyroidism fol-

lowing cessation of treatment. Four of these patients, however, have complained of fatigue and exhibited slightly subnormal basal metabolic rates at intervals of 3 to 24 months following withdrawal of treatment.

Examination of data in Group 2 (a) and (b) reveals no reliable criteria by which ultimate failure to show sustained remission following cessation of therapy could have been predicted. This group contained the only patients showing severe ophthalmopathy. There was, however, no significant difference in the age distribution, type of goiter, or severity of thyrotoxicosis between Groups 2 (a) and 2 (b) on the one hand, and Group 1 on the other. It should be emphasized, however, that the small size of the groups renders statistical comparison of little value.

The high incidence of complicating disease and the higher age incidence in Group 3 suggest that these factors may have influenced the unsatisfactory response to treatment.

We have observed no gross evidence suggestive of malignant degeneration in any case although 5 patients with nodular goiters have not been operated upon, and any of these glands might conceivably contain malignant areas. Five patients were ultimately subjected to thyroidectomy, and in none of these glands was there gross or histologic evidence of malignancy. Two of these goiters were nodular, 2 were diffuse, and 1 was an irregular postoperative regrowth. In addition to prolonged thiouracil therapy, iodine had been administered to all 5 patients immediately prior to operation. After reviewing the histologic sections Dr. R. C. Horn has written the following summary: 'The 2 nodular goiters in this group do not show any unusual findings and in neither case are histologic evidences of hyperplasia seen in the sections taken. The other 3 cases show changes characteristic of diffuse hyperplastic goiters, except for the fact that 1 is complicated by the presence of an adenoma. These 3 cases are not entirely similar, however,

varying just as do hyperplastic goiters not treated with thiouracil. One case shows well-marked involution and, in the goiter associated with an adenoma, the hyperplasia is as marked and active as it is in many toxic goiters prepared for operation with thiouracil alone. However, this degree of histologic change is by no means unknown in iodine-treated goiters. It is interesting to speculate upon the question of whether thiouracil may have stimulated (or even initiated) the growth of the adenoma found in 1 of the goiters in this group."

From the evidence presented by our data it would appear that prolonged treatment with thiouracil does not produce sustained post-therapeutic remission in a sufficiently high percentage of cases of thyrotoxicosis to compare favorably with the results obtainable by expertly performed thyroidectomy or even by irradiation. The best results appear to have been obtained in uncomplicated cases of mild to moderate severity with slight or moderate diffuse thyroid enlargement. It would appear justifiable to undertake prolonged thiouracil treatment in such cases, provided the patient is carefully selected with regard to their intelligence, their willingness and ability to remain under close supervision, their economic status, and their understanding of the potential dangers of toxic reaction to the drug. Prolonged treatment with

thiouracil would also seem justifiable in patients who refuse thyroidectomy or in whom the risk of operation is for any reason unacceptable.

Summary. 1. Thirty-five thyrotoxic patients have received treatment with thiouracil for periods varying from 1 to 19 months. These patients have been observed for intervals varying from 7 to 30 months.

2. Sixteen patients (45.7%) have remained in remission for periods varying from 3 to 29 months following withdrawal of therapy. Nine patients (25.7%) have remained in remission for 1 year or more.

3. The majority of the patients showing sustained post-therapeutic remission suffered from uncomplicated thyrotoxicosis of mild or moderate severity, with slight or moderate diffuse thyroid enlargement.

4. Four patients relapsed following withdrawal of the treatment, but ultimately showed sustained post-therapeutic remissions following readministration of the drug.

5. Eleven patients (31.4%) were maintained in remission for periods varying from 6 to 19.5 months while receiving thiouracil. Two patients (5.7%) relapsed following a reduction in dosage to 0.2 gm. or less per day.

6. The majority of the 6 patients who failed to respond to prolonged treatment were in the older age groups and suffered from complicating diseases.

Since the preparation of this report, Beierwaltes and Sturgis (Remissions in Thyrotoxicosis After Discontinuing Thiouracil, *J. Am. Med. Assn.*, 131, 735, 1946) have published observations on 45 patients with toxic diffuse goiter treated with thiouracil. Twenty-nine of their patients were followed for 4 months or longer. They conclude that persistent post-therapeutic remission may be anticipated in 60 to 80% of such cases if treatment is continued for 10 months or longer.

We are indebted to Dr. Stanton Hardy of the Lederle Laboratories for his generosity in supplying us with thiouracil; to Dr. R. C. Horn for pathologic reports, and to Dr. F. H. Adler and his associates in the Department of Ophthalmology, for their cooperation in periodic eye examinations of many of our H. U. P. patients.

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THE RELATIONSHIP OF BROMSULPHALEIN RETENTION TO THE FEVER OF NATURAL P. FALCIPARUM MALARIA

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DURING a study⁷ of the effectiveness of atabrine intravenously administered in the treatment of *P. falciparum* malaria the question arose whether a single large dose of the drug produced any evidence of hepatic dysfunction. Impairment of hepatic function and necrosis of liver cells have been reported in experimental animals receiving large doses of atabrine.¹¹ To answer the question, the bromsulphalein test was performed in a series of cases of *P. falciparum* malaria before and after treatment. It soon became evident that the excretory function of the liver, as indicated by retention of dye in the blood stream, was impaired during the malarial attack before atabrine was administered, and that the impairment gradually disappeared as the attack responded to treatment. Additional dye retention, due to the atabrine, either did not occur or else was so transient and so overshadowed by that due to the malaria itself that it was not detectable. It was then decided to learn more about the impairment of dye excretion in malaria by performing the test at various times during and after the attack. The data obtained from such observations are contained in this report together with the results of the test in subjects in whom fever was induced by means of typhoid vaccine.

In the recent literature on liver function tests in malaria there are a number of studies in therapeutic as well as natural malaria. Most of them deal with *P. vivax* infections. Bromsulphalein retention has been reported both during and after induced malaria for the treatment of central nervous system syphilis^{2,3,5} and also in

natural malaria.^{4,6,9} Other evidences of hepatic dysfunction have likewise been reported; these include a diminished hippuric acid excretion,^{5,6,8} a decrease in total cholesterol^{3,5} and its esterified fraction,⁵ positive cephalin flocculation tests,^{2,3,5,6,7,10} an increase in serum bilirubin^{2,4,6} and an increase in urobilinogen excretion.²

Procedure. The 33 subjects were Chinese soldiers in the India-Burma theater. Each of them had a positive smear for *P. falciparum* malaria. The bromsulphalein test was performed in all cases while the patient was febrile, immediately before instituting treatment. After therapy was begun, tests were performed at intervals of 1 to 2 days until retention of dye no longer was demonstrable. In a few cases in whom relapses were expected, it was possible to perform the test during the afebrile period immediately preceding the next bout of fever.

The antimalarial drugs used were atabrine dihydrochloride, administered intravenously or intramuscularly, and SN 6911 bisulphate intravenously. SN 6911 administered intravenously and atabrine administered intravenously or intramuscularly are equally effective in terminating fever and parasitemia in the average case of *P. falciparum* malaria. When used intravenously, the 0.6 or 0.8 gm. dose of atabrine was dissolved in distilled water (0.2 gm. per 10 cc.) and the resulting solution placed in 1000 cc. of physiologic saline solution. This preparation, freshly made, was then administered by intravenous drip over a period of 3 to 4 hours. A dose of SN 6911 bisulphate (0.64 gm.) equivalent to 0.6 gm. of the base was dissolved in 1000 cc. of physiologic saline and administered in the manner similar to that used for atabrine. When atabrine was given intramuscularly, the desired dose (0.4 to

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0.6 gm.) was dissolved in distilled water (0.2 gm. in 10 cc.) and one-half the total amount injected into each buttock. The amount of bromsulphalein injected was calculated on the basis of 5 mg. per kilo of body weight and the test sample was taken from the opposite arm 30 minutes after the injection. The mean weight of the subjects

whether or not dye retention could be produced by artificially induced fever, the test was performed before, during and after induction of fever by the injection of 1 cc. of triple typhoid vaccine (50,000,000 organisms, Indian strain) in apparently normal individuals.

TABLE 1.—CLINICAL AND THERAPEUTIC DATA ON THE CASES ON WHOM THE BROMSULPHALEIN TESTS WERE DONE

Case No.	Before treatment		Day of disease on which treatment was given	Type of drug	Amount of drug (gm.)	Route of administration	Day on which smear first became negative after day of treatment
	Degree of parasitemia	Degree of splenomegaly					
1 . . .	2	0	3	A*	0.6	I.V.	2
2 . . .	1	3	4	A	0.6	I.M.	1
3 . . .	1	1	1	A	0.8	I.V.	2
4 . . .	2	1	11	A	0.6	I.V.	2
5 . . .	2	1	4	A	0.8	I.V.	2
6 . . .	3	3	8	A	0.6	I.M.	2
7 . . .	2	0	4	A	0.5	I.M.	2
8 . . .	2	1	4	A†	0.4	I.M.	2
9 . . .	1	1	5	SN†	0.6	I.V.	1
10 . . .	2	1	8	SN	0.6	I.V.	3
11 . . .	2	1	3	SN	0.6	I.V.	3
12 . . .	2	0	2	SN	0.6	* I.V.	3
13 . . .	1	0	3	A	1.0†	I.M.	1
14 . . .	3	1	4	SN	0.6	I.V.	3
15 . . .	2	1	2	SN	0.6	I.V.	2
16 . . .	3	1	2	A	0.4	I.M.	2
17 . . .	1	1	1	A	0.6	I.V.	1
18 . . .	2	3	2	A	0.4	I.M.	2
19 . . .	2	0	2	A	0.4	I.M.	2
20 . . .	2	0	2	A	0.4	I.M.	2
21 . . .	1	0	6	A	1.0†	I.M.	2
22 . . .	3	0	3	SN	0.6	I.V.	4
23 . . .	1	1	3	SN	0.6	I.V.	2
24 . . .	1	1	8	SN	0.6	I.V.	1
25 . . .	1	0	4	SN	0.6	I.V.	2
26 . . .	1	1	5	SN	0.6	I.V.	2
27 . . .	2	0	4	SN	0.6	I.V.	2
28 . . .	1	1	3	A	0.8	I.V.	1
29 . . .	2	0	3	A	0.8	I.V.	2
30 . . .	1	0	2	A	0.4	I.M.	2
31a . . .	2	0	3	A	0.6	I.V.	2
31b . . .	2	0	4	A	1.0†	I.M.	5
32a . . .	3	1	4	SN	0.6	I.V.	3
32b . . .	1	1	1	A	1.0†	I.M.	3
33a . . .	4	1	4	SN	0.6	I.V.	3
33b . . .	4	1	1	SN	0.6	I.V.	2

* A, atabrine dihydrochloride.

† SN, SN 6911 base.

‡ 0.4 gm. on 1st day, then 0.2 gm. daily for 3 days.

was 56.3 (range 47 to 68.1) kilos. The standards used were prepared on the basis of the 5 mg. of bromsulphalein per kilo of body weight test dose. Daily thick smears for malaria parasites were made, examined and graded on the basis of +1 (rare to few), +2 (moderate number), +3 (many), +4 (loaded). Oral temperatures were taken at 4 hour intervals. In order to determine

RESULTS. There was retention of bromsulphalein during the febrile period in all 36 attacks of malaria in 33 subjects. The retention ranged from 5 to 50% and averaged 16.6%. It disappeared in 23 of the 36 attacks within 96 hours, and in 9 attacks within 96 to 192 hours after the institution of therapy. In the remain-

ing 4 attacks, which were associated with mild scleral icterus (Cases 8, 11, 22 and 27), the retention decreased but did not clear up entirely during the 8 days observation period following therapy (Tables 1 and 2, Fig. 1). The average duration of fever after the institution of therapy

because in each case a recent attack of malaria had been treated with an inadequate amount of atabrine, and the patient was being retained in the hospital in expectation of a recurrence. Cases 12, 25, 31*b*, 32*a* and 33*b* had no retention before they became febrile. In 3 other patients,

TABLE 2.—RESULTS OF THE BROMSULPHALEIN TEST BEFORE AND AFTER TREATMENT

Case No.	Temperature in ° F. at time of test immediately before instituting treatment	Duration of fever in hours after beginning treatment	Immediately before treatment	After treatment									
				Time in days									
				1	2	3	4	5	6	7	8		
1 103.2	16	15	..	5	..	0						
2 102.2	20	5	..	0								
3 104.2	36	15	..	5	0	0						
4 104.2	32	35	20	10	5	0						
5 103.8	32	50	20	8	..	0						
6 103.2	16	10	..	0								
7 104.8	36	20	..	5	0							
8 105.5	28	28	..	8	5	..	10	5		
9 105.5	16	12	..	0	0					
10 104.5	12	15	0							
11 105.0	20	15	..	10	5	..	5	3		
12 103.5	24	7	5	..	0					
13 105.0	84	25	20	..	10	..	5	0				
14 104.2	80	35	..	18	..	10	..	5	0	0		
15 104.2	28	15	..	12	..	10	2	0				
16 104.0	40	12	10	10	0		
17 104.0	28	5	..	0								
18 103.5	20	10	5	0								
19 103.5	36	15	10	5	0							
20 101.2	24	10	0							
21 105.2	16	22	10	5	0	0						
22 105.2	40	30	20	13	10	10	7	11	8	5		
23 102.5	36	15	8	5	0	0						
24 103.5	16	10	15	10	5	0						
25 104.2	32	8	0	0								
26 105.5	32	5	0									
27 105.2	72	50	50	50	50	20	..	15	..	5		
28 104.0	16	10	5	0	0	0	0					
29 103.2	24	10	..	5	0	0	0					
30 104.0	36	25	15	10	5	0	0					
31 <i>a</i> 104.2	24	15	..	5	0							
31 <i>b</i> 101.2	20	20	7	0	0							
32 <i>a</i> 106.0	36	6	..	0								
32 <i>b</i> 105.0	12	9	..	0								
33 <i>a</i> 104.0	64	15	..	6	..	0						
33 <i>b</i> 102.5	40	5	..	0								

Cases 8, 11, 22 and 27 had evidence of mild jaundice. Cases 12, 25, 31*b*, 32*a*, 32*b* and 33*b* had no retention of dye before they became febrile.

was 31.7 (range 12 to 84) hours. The smear in the average case was negative on the 2.1 (range 1 to 5) day. Thus the dye test became negative 47.6 (range 8 to 152) hours after the fever subsided.

In 6 instances bromsulphalein tests were performed before, during and after malarial fever. The pre-fever test was possible

Cases 10, 13 and 24, a retention of 2, 3 and 5% was observed when the test was performed during the onset while the daily temperature undulations were low (98.6 to 100.5° F.). Subsequently when the fever became higher (103.5° to 105° F.) the retention increased to 15, 25 and 10% respectively. The observations on the

above 9 cases demonstrated that dye retention was absent before, slight while the fever was low, and more marked after the malarial fever became well established.

The degree of dye retention in the average case appeared to depend on the severity of the infection as judged by the length of time the patient had had fever prior to receiving therapy as well as by the length of time it took for the temperature to become normal after institution of treatment. The average dye retention in 19 cases who had fever for 1 to 3 days was 13.8% (range 5 to 30) as compared to 21% (range 5 to 50) for

tion in the former group (23 attacks) was 18.3% (range 6 to 50) as compared to 14% (range 5 to 50) in the latter (13 attacks). There appeared to be no correlation between the degree of dye retention and the presence or absence of splenomegaly, anemia or the speed at which the parasites disappeared from the peripheral blood after treatment was started.

In the 3 subjects in whom fever was induced artificially by means of typhoid vaccine, the test revealed no dye retention on the day prior to induction of fever. During the height of the fever, retention of 15 to 20% occurred in all 3 instances.

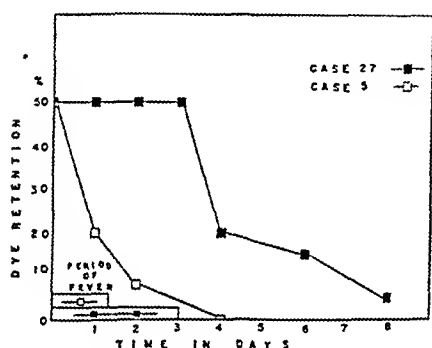


FIG. 1

FIG. 1.—A comparison of the dye retention curves reveals a more prolonged period of dye retention in Case 27 who had seleral icterus prior to institution of therapy. Treatment in both cases was administered on day (O). A similar prolonged period of dye retention was also observed in Cases 8, 11 and 22 (Table 2) who had seleral icterus but in whom the fever subsided more promptly in response to therapy than in Case 27.

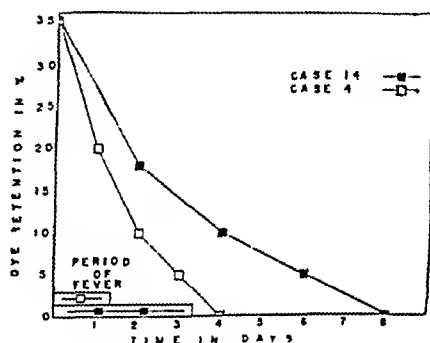


FIG. 2

FIG. 2.—A comparison of the dye retention curves reveals that the test became negative more promptly in Case 4 than in Case 14. Case 4 had a less severe infection as judged by a more prompt subsidence of fever in response to therapy which was instituted on day (O) in both instances.

17 cases who had fever for 4 or more days. In the 11 cases who had retention of 20% or more, the average duration of fever after the beginning of therapy was 43.2 (range 16 to 84) hours as compared to 26.7 (range 12 to 64) hours for the remainder who had 15% or less (Table 2, Fig. 2). There was no remarkable correlation between the degree of dye retention and the height of fever prior to therapy in individual cases, although the average dye retention in cases with temperatures of 104° F. or more was slightly greater than in those with temperatures less than 104° F. The average dye reten-

The period of induced fever lasted 7 to 9 hours. Tests, performed at 1 to 2 day intervals thereafter, revealed a gradual decrease in retention until it was no longer demonstrable on the 3rd to the 4th post-febrile day (Table 3, Fig. 3).

COMMENT. The following observations suggest that the dye retention observed in *P. falciparum* malaria is related to the fever: (1) retention was absent before fever occurred, slight during the low febrile state of the onset stage, more marked at the height of the fever, and disappeared within a few days after the fever subsided in response to therapy;

(2) retention was more persistent in those cases in whom the infection was more severe; (3) dye retention was produced by artificially induced fever in apparently normal subjects.

The demonstration of transient dye retention in all of our non-jaundiced malarial patients and of the failure of the dye test to become negative in cases with mild scleral icterus as promptly as in those without clinical icterus, indicates that most cases of malaria have a transient

may exist because the liver becomes palpable in a large percentage of cases of *P. falciparum* infection during the febrile stage. The enlargement disappears as the attack subsides. Central and mid-zonal atrophy or necrosis have been observed in the sections of livers of fatal cases.⁴

In comparing the results reported in this communication with those of others, it should be kept in mind that our patients had natural *P. falciparum* malaria, that

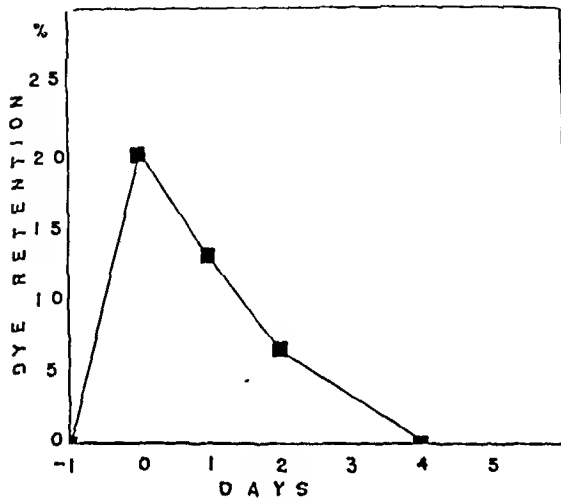


FIG. 3

FIG. 3.—Curve of dye retention in subject who had fever induced on day (0) by means of typhoid vaccine. The period of fever lasted 8 hours.

FIG. 4.—The fever curve and results of the bromsulphalein test in Case M. F., admitted to the University of Pennsylvania Hospital. The patient developed an attack of *P. vivax* malaria 4 months after discontinuing atabrine suppression treatment. He presumably contracted the infection in the I. B. theater. The febrile spikes in the figure are the third and fourth of the attack. Antimalarial treatment was started at the height of the last febrile spike. The curves clearly show that the dye retention is greatest when the patient is febrile. They also show that when the amount of dye in the blood stream is determined 45 minutes after injecting the test dose, very little or no retention may be found when the 30 minute sample still shows retention. On the 10th postfebrile day (indicated by arrow), when the 30 minute blood sample showed a 2% retention and the 45 minute sample was negative, the thymol turbidity (3.5 units) and flocculation (+2) tests were positive. The thymol tests provided additional evidence that the disease process affecting the liver was still slightly active.

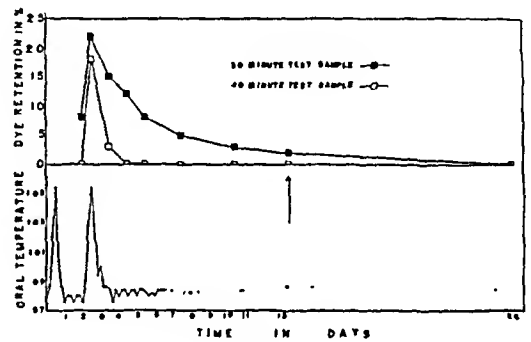


FIG. 4

impairment of dye excretion, but that some cases may have a more persistent impairment. It may be that both groups have the same hepatic lesion but in different degrees of severity. The development of moderately severe, non-hemolytic jaundice has been noted in therapeutic malaria^{1,5,10} and does occur in natural malaria. We have no evidence of the nature of the microscopic changes in the liver during an ordinary attack of malaria. It is logical to assume that some changes

the initial dye tests were performed while the patients were febrile, and that the amount of dye remaining in the blood stream 30 minutes after injecting the test dose was determined. Practically all of the reports in the literature on the bromsulphalein test in malaria have been on induced or on relapsing *P. vivax* malaria. These are characterized by a different type of fever curve than that which occurred in our cases in whom the fever was of the sustained type and which, despite

daily undulations, rarely dropped to normal until the attack was terminated. In relapsing or in induced *P. vivax* malaria, the temperature curve is characterized by febrile spikes on alternate days, the intervening days being free of fever. If the dye test is performed on an afebrile day, there is apt to be less dye retention than when the test is performed during the febrile spike. Furthermore, if one determines the amount of dye remaining in

reported by Lippincott and his associates.⁶ An additional factor was their failure to differentiate significant low degrees of retention from those which they considered of no significance because similar values were found in their control subjects.

Summary. Retention of injected bromsulphalein dye was observed in cases of natural *P. falciparum* malaria. Retention was absent during the prefebrile stage, slight during the onset and moderate dur-

TABLE 3.—BROMSULPHALEIN RETENTION BEFORE, DURING AND AFTER ARTIFICIALLY INDUCED FEVER

Case No.	Maximum oral temperature attained	Duration of fever (hours)	Bromsulphalein retention (%)					
			Before induction of fever	At height of fever	Time in days after day on which fever was induced			
					1	2	3	4
A	101 0	8	0	20	13	6		0
B	101 6	7	0	15	10		5	0
C	101 2	9	0	15	10	tr.	0	

the blood stream 45 minutes after the injection of the test dose on an afebrile day, there may be little or no retention, whereas a 30 minute test sample may show significant retention (Fig. 4). The determination of the amount of dye in the 45 minute sample of blood, as well as the performance of the test on afebrile days may be at least 2 of the factors responsible for the low incidence of positive tests in relapsing *P. vivax* malaria

ing the height of the fever. It disappeared in 2 to 3 days after the fever subsided in response to therapy. The greater dye retention was present in cases in which the fever was higher or had lasted a longer time, and in those who responded less promptly to therapy. The dye retention was reproduced in apparently normal subjects by inducing fever by means of typhoid vaccine.

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RHEUMATOID ARTHRITIS

IV. HEMOLYTIC STREPTOCOCCUS PRECIPITIN REACTIONS*

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DISSATISFACTION with the obscurity of the rôle of the hemolytic streptococcus in the pathogenesis of rheumatoid (atrophic) arthritis has prompted a search of the patients' sera for precipitins against various streptococcal fractions. Reports have appeared on reactions with the following as test antigens: nucleoprotein fractions designated "D" and "K",^{3,9} the C-carbohydrate characteristic of Group A,^{3,9} the same C-carbohydrate more highly purified,^{1,2} crude extracts (by Lancefield's heat and HCl method⁶) of streptococci of Group A,^{1,2,7,8} an alcohol-precipitable fraction from crude extracts of Group A⁸ and crude extracts of Groups B through G.^{1,2} With all the various fractions of the Group A hemolytic streptococcus, rheumatoid arthritis sera were found to react more strongly than did control sera from patients who had neither rheumatoid arthritis nor a recent streptococcal infection. Testing arthritis sera against extracts of other groups, Dawson and Olmstead² noted occasional reactions which were regarded as lacking significance. They concluded that the "precipitin reactions in rheumatoid arthritis sera are characteristic for Group A hemolytic streptococci." Chasis and McEwen¹ found a higher incidence of "cross-reactions" between arthritis sera and extracts of groups other than A. These reactions they attributed to an antigenic constituent common to the various groups.

Recent observations¹¹ have cast doubt upon supposedly specific reactions in which the serum of this disease takes part. We have therefore reexamined the foregoing experimental results and their interpretations. Because they help to illuminate

the behavior of rheumatoid arthritis serum, the precipitin reactions with crude extracts of streptococcal Groups B through G will be taken up first, with special attention to the saline control tube. The reactions of arthritis sera with Group A fractions will then be reevaluated.

Materials. Bacteria and Culture Media. The Group A hemolytic streptococcus strains Tho and Atk were freshly isolated and apparently pathogenic. They were provided by the Laboratory of the Philadelphia General Hospital. The Group B strain K151A was furnished by Dr. Stuart Mudd, and the Group C strain Hen and the Group D strains C1 and C745 by Dr. Ruth Miller. Dr. Rebecca Lancefield supplied the remaining strains: Group B, V8; Group C, K104; Group E, K131 and K129; Group F, F67 and H127; Group G, D166B and F68A. We wish to thank all these donors. The media for keeping stock cultures and for growing organisms for extractions were those previously described.¹² The stocks were subcultured once in 3 months.

Crude Extracts of Hemolytic Streptococci. Ten cc. of the tryptone glucose yeast-extract broth in a test-tube were inoculated with 1 cc. of stock culture and the tube was placed in a water-bath at 37° C. The level of water in the bath was at about one-third the height of the broth, in order to speed convection currents. After 6 hours this seed culture was added to 500 cc. of the same broth in a 2 liter Erlenmeyer flask, which was (air) incubated overnight. The culture was then plated for purity. The bacteria were collected in the centrifuge and extracted by Lancefield's⁶ method (resuspended in 10 cc. of N/20 HCl in saline; boiling water-bath 15 minutes; supernatant neutralized and precipitate discarded). "Merthiolate" (sodium ethyl mercuri thiosalicylate, Lilly)

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TABLE 1.—PRECIPITATION OF CRUDE EXTRACTS OF HEMOLYTIC STREPTOCOCCI OF VARIOUS GROUPS WITH RHEUMATOID ARTHRITIS SERA

Patient	Age of patient (yrs.)	Duration of disease (yrs.)	Group A		Group B		Group C		Group D		Group E		Group F		Group G		Control	Age of serum (days)
			Tho	Mk	V8	K151A	K104	Hen	C1	C745	K131	K129	F67	H127	D166B	F68A		
1. Bat	53	1	..	?	0	..	0	..	0	..	0	..	0	..	+	..	0	53
2. Bar	50	3	..	?	0	..	0	..	0	..	0	..	0	..	+	..	0	53
3. Bro	69	3	..	+	0	..	0	..	0	..	0	..	0	..	+	..	0	53
4. Kep	40	4	0	..	0	..	0	..	0	..	0	..	+	..	0	49
5. Har	46	7	0	..	0	..	0	..	0	..	0	..	?	..	0	53
6. Cos	63	18	0	0	0	..	0	..	0	0	77
7. Sak	44	1+	+	+	..	0	0	0	0	0	0	0	0	0	..	fl tr	0	5
8. Les	33	1½	+	0	..	?	?	0	..	0	..	0	0	0	..	+	0	27
9. Mac	42	1	0	0	..	0	0	0	0	0	0	0	0	0	..	fl tr	0	1
10. Rov	56	1	0	0	..	0	0	0	0	0	0	0	0	0	..	?	0	27
11. Sel	46	6	+	+	..	0	0	0	0	0	0	0	0	0	..	?	0	5
12. Pay	55	7	+	+	..	0	0	0	0	0	0	0	0	0	..	+	0	30
13. Sav	36	7	+	+	..	0	0	0	0	0	0	0	0	0	..	+	0	4
14. Jon	60	10+	+	+	..	0	0	0	0	0	0	0	0	0	..	+	0	2
15. Ink	39	10+	+	+	..	0	0	0	0	0	0	0	0	0	..	+	0	29
16. Hal	36	11	0	0	..	0	0	0	0	0	0	0	0	0	..	?	0	4
17. McG	49	16	0	0	..	0	0	0	0	0	0	0	0	0	..	fl tr	0	29
18. Con	60	40*	+	+	..	0	0	0	0	0	0	0	0	0	..	fl tr	0	2
19. Row	70	1½	+	+	0	+	0	0	0	0	0	0	0	0	..	0	0	27
20. Don	34	5	+	+	0	+	0	0	0	0	0	0	0	0	..	fl tr	0	27
21. Pol	41	5	+	+	..	+	+	+	+	+	0	..	+	+	..	+	fl tr	40
22. Lak	29	10	+	+	..	+	+	+	+	+	..	+	+	+	..	+	fl tr	5
23. Gre	29	16	+	+	..	+	+	+	+	+	..	+	+	+	..	+	?	51
24. Glo	50	11	+	+	..	+	+	+	+	+	..	+	+	+	..	+	0	1
25. Gal	66	30	+	+	..	+	+	+	+	+	..	+	+	+	..	+	fl tr	19
26. Sco	40	6	+	+	0	?	0	0	0	0	0	0	0	0	..	+	+	2
27. Tho	53	7+	+	+	fl tr	..	0	0	0	0	0	0	0	0	..	+	+	4
28. Pos	55	10	+	+	..	+	+	+	+	+	..	+	+	+	..	+	+	29
29. McN	70?	10	+	+	0	..	0	0	0	0	0	0	0	0	..	+	0	1
30. Bra	56	12	+	+	..	0	0	0	0	0	0	0	0	0	..	+	fl tr	2
			+	+	..	0	0	0	0	0	0	0	0	0	..	+	0	20

These tests were centrifuged

These tests were centrifuged.

? = possible fine flakes, indefinite even with reading glass.

fl tr = (flakes, a trace) fine flakes whose presence was suspected with the unaided eye and confirmed with the reading glass.

+ = the smallest flakes whose presence was certain with the unaided eye.

++ = a few large flakes, clear fluid.

0 = negative

in final concentration 1:10,000 was added as preservative.

C-substance, the Group-specific Carbohydrate of Group A Hemolytic Streptococcus. A supply of this polysaccharide as prepared and purified by the method of Zittle and Harris¹³ was kindly provided by Dr. T. N. Harris, to whom our thanks are due.

were incubated in a water-bath at 37° C. for 2 hours, refrigerated overnight, centrifuged at 1700 r.p.m. for 10 minutes, and read. The stronger of the precipitates in each pair of antigen tubes is recorded. This was usually in the tube containing 0.2 cc. of antigen.

For the tests recorded in Table 3, 2×10^{-5}

TABLE 2.—PRECIPITATION OF CRUDE EXTRACTS OF GROUPS A AND G BY NON-ARTHRITIS SERA

Patient	Age of serum (days)	Group A Tho	Group G D166B	Saline control	Patient	Age of serum (days)	Group A Tho	Group G D166B	Group G F68A	Saline control
1. Mat	52	o	?	o	19. Sel	56	?	+	..	o
2. Bar	51	+++	+	o	20. Ste	56	o	fl tr	..	o
3. Wea	51	+	++	o	21. Val	56	+ =	+	..	o
4. Cra	51	+	o	o	22. Spe	2	o	..	?	o
5. Mon	54	o	?	o	23. Kee	2	o	..	+	o
6. Maz	52	o	?	o	24. Rob	2	o	..	++	o
7. Kan	54	o	o	o	25. And	2	o	..	o	o
8. Mor	54	o	+	o	26. Sty	2	=	..	?	o
9. Bru	51	o	fl tr	o	27. For	2	o	..	+	o
10. Axl	54	+++	+++	o	28. Moe	2	o	..	+	o
11. Hop	54	?	fl tr	o	29. Nar	1	++	..	+++	o
12. McN	52	?	++	o	30. Pri	1	+	..	+++	o
13. Cha	52	o	o	o	31. Lut	1	+	..	=	o
14. Vec	57	+	++	o	32. Cla	1	o	..	o	o
15. Has	56	o	=	o	33. Lan	1	=	..	+	o
16. Hal	56	o	o	o	34. Tru	1	o	..	o	o
17. Har	56	fl tr	+	o	35. Hog	1	o	..	o	o
18. Fer	56	o	++	o						

These tests were centrifuged.
Symbols as in Table 1.

TABLE 3.—PRECIPITATION OF C-SUBSTANCE OF GROUP A HEMOLYTIC STREPTOCOCCUS BY REPRESENTATIVE ARTHRITIS SERA

Antigen gamma	Glo	Gal	Gre	The	Pay	Szk
0.5	f h = =	v = = = =	o = = + +	vffvtt =	ovfff = =	oooovvv
0.05	t = + +	v + + + +	o t t = =	?fftt =	ofttt = =	ovff ttt
0	f f t h	? ? v v f	o ? v v v	o?vvvvf	oo??ov v	oooo?o?

Antigen gamma	McG	Sel	Lak	Har	Hak	Bat	Haf
0.5	oo??vvvvv	hhh h h h h	oo??ovv	ooooooo	oooooooovv	ooooooo	ooooooo
0.05	ooo?vffft	hhh = = = =	ovffflht	oo?vfff	ooo?vffftf	ooooooo	ooooooo
0	ooo?vvv?v	hhh h h h h	o?vvvff	ooovvvv	oooooo??v	ooovvf	ooooooo

These tests were not centrifuged. The columns of symbols recorded for each serum represent readings at successive daily intervals beginning 1 day after the tests were set up.

Interpretation of symbols:

Visible only with reading glass:

o = negative

? = doubtful

v = very faint trace

f = faint trace

t = trace

h = heavy trace

Without reading glass:

= = weakest visible

+ = next stronger

Sera. These have been described elsewhere.¹² Additional sera from patients with typical rheumatoid arthritis were obtained in the Dispensary of the Jefferson Hospital. The donors of non-arthritis serum were free from known recent hemolytic streptococcal infection.

Methods. Precipitation Tests. In the tests recorded in Tables 1 and 2, each antigen was used in amounts of 0.2 and 0.05 cc. These volumes were made up to 0.4 cc. with physiologic salt solution. The saline control tube contained 0.4 cc. of physiologic salt solution without antigen. One-tenth cc. of serum was added to each tube. The tests

and 2×10^{-6} dilutions of antigen were used. The procedure otherwise was as above through the overnight refrigeration. Daily readings without centrifugation were made by the method previously described.¹²

EXPERIMENTAL. *Precipitation with Crude Extracts of Groups Other Than A.* The sera in Table 1 have been grouped to show that the positive reactions between arthritis sera and crude extracts of Groups B through F tend to be of an *all or none* character. A positive reaction with any of these groups is apt to be

accompanied by positives in others. Furthermore, we wish to emphasize the fact that all are negative only when the saline control is frankly negative, as in the first 18 sera.

The sera numbered 26 through 29 illustrate the relation of age of serum to the response in the saline control and hence to the reactions with extracts of Groups B through F. When tested early the reactions with saline and with bacterial extracts were both negative. After the lapse of some weeks both were positive.

Table 1 also shows that the reactions with extracts of Groups B through F not only tend to become positive when the saline tube is positive, but often show *stronger* positives than the latter.

From Table 1 the following inferences may be drawn: 1. Rheumatoid arthritis sera do not precipitate with crude extracts of hemolytic streptococci of Groups B through F provided the saline control tube is frankly negative.

2. When precipitation with saline occurs, the precipitate with bacterial extracts is apt to be even stronger than with saline.

The importance of these factors in interpreting precipitin reactions involving rheumatoid arthritis serum is obvious. In this connection, 2 generalizations become probable: 1. The precipitation of arthritis serum by saline may be enhanced by non-specific adsorption of a heterologous antigen. This could be mistaken for a genuine antigen-antibody reaction.

2. By this mechanism of enhancement, a serum might appear negative in the saline control tube and weakly positive in the presence of heterologous antigen. Misinterpretation would be still more likely in this case.

The high incidence of positive reactions between crude extracts of streptococci of Group G and arthritis sera loses significance in view of the frequency of positive reactions between these extracts and non-arthritis sera, shown in Table 2. Precipitins for Group G were not found in control sera by Dawson and Olmstead² or Chasis

and McEwen,¹ presumably because of differences in the strains used.

Precipitation with Crude Extracts of Group A. The interpretation of the reactions between arthritis sera and crude extracts of Group A as reported in the literature is complicated by the question of the response of control sera. Reports of the ability of control sera to precipitate crude extracts of Group A present conflicting evidence. Thus, there is 1 report⁷ of positive results in 24% of sera from 21 normal persons; another,¹ 6 normal sera, all negative; another,² 32 non-arthritis sera with strong precipitins only after streptococcal disease; and another,⁸ 22 normal sera, all negative. The last-named tests alone were not centrifuged. Our own observations of centrifuged tests, shown in Table 2, are in agreement with the first-named, i. e., about one-quarter of individuals who have neither rheumatoid arthritis nor a recent hemolytic streptococcal infection may be expected to have in their sera precipitins for crude extracts (of selected strains) of hemolytic streptococci of Group A.

Strain differences may account partially for the discrepancies in the reported results with control sera. Upon repeating the work of Neil and Hartung³ on the reaction of rheumatoid arthritis sera with antigens precipitable by 3 volumes of alcohol from crude extracts we found that the same sera do not respond equally well with antigens prepared from different strains of Group A hemolytic streptococcus. Freshly isolated pathogenic strains gave the strongest results. On 2 occasions, strains lost this reactivity after about 10 months as laboratory stocks.

Comparison of the Group A columns in Tables 1 and 2 shows that, while some non-arthritis sera have greater ability to precipitate a crude Group A extract than some arthritis sera, arthritis sera generally have more potency in this respect than non-arthritis sera, even when the saline control tube is negative.

Precipitation with C-substance of Group A. Although crude extracts of Group A

organisms contain C, the precipitates recorded in Table 2 are due to antibodies other than anti-C. The alcohol-precipitable antigen of Neil and Hartung⁸ has essentially the same serologic activity with arthritis and non-arthritis sera as its parent crude extract, but it contains no C, provided the original crude was prepared by the Lancefield⁶ HCl method. (When the crude is obtained by Fuller's⁴ hot formamide extraction of microorganisms, the 3-volume alcohol precipitate will contain some C. Formamide at 150° C. is a much more efficient agent for bacterial disintegration than N/20 HCl at 100° C., and 3 volumes of alcohol will precipitate some C from a solution rich in C, but not from one poor in C.) The absence of C in a 3-volume alcohol precipitate from a HCl extract is shown by its failure to react with rabbit antiserum (Lederle) containing anti-C, prepared by immunization with the whole streptococcus. The C-substance can be precipitated from this alcohol supernate by the addition of an equal volume of acetone. When redissolved in a volume of saline equal to that of its parent crude extract, its optimal zone for precipitation with rheumatoid arthritis serum is more than 40 times as dilute as that of the original crude extract as set up in Table 1. This indicates that the results shown in the Group A column of Table 1 are not due to anti-C.

Rheumatoid arthritis serum tends to give a more delicate precipitate with the C-substance than with a crude extract of Group A. In estimating its ability to precipitate C we have resorted to the method used previously¹² for antibodies against a pneumococcus carbohydrate fraction. In this procedure, prolonged observation with special visual aids is substituted for centrifugation. Sera from 26 patients with typical rheumatoid arthritis were examined in this way. Characteristic results are shown in Table 3. All the observed types of response are represented in the table. It will be noted that whenever precipitation occurred with the antigen, the saline control tube failed

to remain frankly negative, usually becoming positive within 1 day or 2. The precipitate in the presence of C exceeded that in the saline control tube by 2 or more gradations in 12 sera (positive), by 1 gradation in 7 sera (weakly positive or doubtful), and did not exceed in 7 sera (negative). Although the precipitation of arthritis serum in saline tends to increase with the age of the serum,¹¹ this factor did not appear to exert a major influence on this experiment, as 8 of the 12 positive sera were not over 1 week old and the negatives included samples up to 83 days old.

The non-arthritis sera which had precipitated with a crude extract of Group A (Table 2) were set up against the same strengths of C as in Table 3. These were made in duplicate: 1 tube was centrifuged at 24 hours; the other was read with the reading glass daily for 9 days and then centrifuged. There was good agreement between the duplicate tubes. Only those sera which were positive upon centrifugation at 24 hours showed precipitates in the prolonged observation, including the centrifugation at 9 days. These positives were 2 in number, from Patients 4 (Cra) and 26 (Sty). The remaining non-arthritis sera, which had given no precipitate with a crude extract of Group A, were then set up against the same amounts of C and centrifuged at 24 hours. All were negative with the exception of 2, which were weakly positive. Of the 15 non-arthritis sera which received prolonged observation with the reading glass, 13 had frankly negative saline control tubes. Particles resembling those frequently seen in arthritis sera occurred in the control tubes of Patient 4 (Cra) (antigen tube positive on centrifugation) and Patient 29 (Nar) (antigen tube negative on centrifugation).

SUMMARY OF EXPERIMENTAL RESULTS. With crude extracts of hemolytic streptococci of Group A, precipitates are formed by some arthritis sera and by some non-arthritis sera. Both the incidence and the intensity of these precipitates are greater with the arthritis sera.

With purified C-substance of Group A, the discrepancy between arthritis and non-arthritis sera is greater, precipitates with the latter occurring much less frequently. However, positive reactions with arthritis sera are usually accompanied by a positive saline control.

With crude extracts of streptococci of Groups B through F, arthritis sera do not give a visible reaction provided the saline control tube is frankly negative. The response of arthritis and non-arthritis sera to crude extracts of the 2 strains of Group G used in these experiments is comparable to the reactions with crude extracts of Group A.

Discussion. Evidence has been presented elsewhere¹² indicating that sera from patients with rheumatoid arthritis have the ability to enhance the action of normally present precipitins for a somatic carbohydrate of the pneumococcus. The occurrence of these precipitins in normal serum is attributable to the frequent presence of the pneumococcus in normal human throats. The same reasoning is applicable to the existence of Group A hemolytic streptococcus precipitins in normal and arthritis sera and their enhancement in the latter.

The human nasopharynx is probably the natural reservoir of the Group A hemolytic streptococcus. Surveying examinations made in different parts of the world, Hare⁵ collected reports of 574 strains of hemolytic streptococci recovered in nasopharyngeal cultures of 3102 presumably normal individuals. The strains which had been grouped were listed as follows: A, 216; B, 15; C, 84; D, 1; E, 0; F and G together (mostly G), 119; H, 27; K, 8. When the predominance of Group A strains in the normal nasopharynx is viewed in the light of the non-specific enhancing property¹¹ of rheumatoid arthritis serum, the conclusion of Dawson and Olmstead² that "precipitin reactions in rheumatoid arthritis sera are characteristic for Group A hemolytic streptococci" no longer connotes a streptococcal etiology for this disease.

The incidence of precipitins in non-

arthritis sera makes the foregoing argument more applicable to the reactions with crude extracts of Group A than to the reactions with the C-substance of Group A. To increase its plausibility in relation to the latter reactions, 3 lines of evidence may be cited:

1. The C-precipitate is inherently less robust than the crude extract precipitate, whether by arthritis or non-arthritis serum. This is probably due in part to its refinement, with the elimination of adsorbable protein impurities. The same explanation presumably accounts for the fact that precipitation of the nucleoprotein fractions D and K^{3,9} is stronger than precipitation of C.

2. Precipitation of C by arthritis serum is more dependent on precipitation in the saline control tube than is crude extract precipitation by the same serum. This suggests that non-specific adsorption of antigen may play a part in these precipitates, once they have been initiated by feeble precipitins.

3. The ability of arthritis sera to precipitate C, as reported by Dawson, Olmstead and Jost,³ varies directly with their streptococcus agglutinin titers. The correlation is not perfect for individual sera, but the trend is unmistakable. As agglutinin titers decrease, C-precipitins (at best, positive in less than half the sera) fall off sharply. The authors interpreted this parallelism as an indication that a genuine antigen-antibody mechanism is operating. However, the parallel can also be interpreted as the result of a non-specific enhancing property influencing both reactions. The same parallel occurs between streptococcus agglutinins and precipitins for crude extracts of Group A.^{2,8} It is likely that other observers^{1,7,9} were guided, perhaps unintentionally, by this parallelism in selecting "representative" arthritis sera for the study of precipitins.

Having the opinion¹⁰ that rheumatoid arthritis is not of streptococcal origin and at the same time confronted with an apparent excess of anti-C in the patients' sera, we have given serious consideration

to the possibility that the disease process might produce in the patient's tissues an abnormal substance which happened to be the antigenic equivalent of C. Because of circumstances which will be described in a subsequent paper, C would fit into such a concept with peculiar facility. However, this concept appears improbable in the light of the interpretation of precipitins presented above.

Summary. The ability of rheumatoid arthritis serum to precipitate crude extracts of Group A hemolytic streptococci appears to be due to an enhancement of the action of normally present antibodies. This enhancement can occur even though the saline control tube is negative. When the non-specific serologic enhancing power of arthritis serum is strong, rendering the saline control tube actually or

potentially positive, precipitates may occur with crude extracts of streptococci of groups other than A. These are interpreted as being due to non-specific adsorption of heterologous antigens. Both factors, the enhancement of action of normally present antibodies and the non-specific antigen adsorption, may be active in the precipitation of arthritis serum with the C-carbohydrate of Group A streptococci, where normal precipitins are feeble. The apparent selectivity of rheumatoid arthritis serum for streptococci of Group A is attributable to the higher incidence of this group as inhabitants of the normal human nasopharynx.

Conclusion. It is unlikely that the sera of patients with rheumatoid (atrophic) arthritis contain a genuine excess of hemolytic streptococcus precipitins.

This work was begun in the Laboratory of the Chestnut Hill Hospital, Philadelphia, under a grant from the Charlotte Drake Cardeza Foundation of the Jefferson Medical College. Our thanks are due to Dr. Thomas Cope, Jr., Director of that laboratory, for his coöperation and to Mrs. Charlotte Sommer for technical assistance. The work was completed at the University of Pennsylvania, under a grant from the National Foundation for Infantile Paralysis, Inc. The use of the facilities of the Harrison Department of Surgical Research and of the Departments of Anatomy and Bacteriology and the technical assistance of Mrs. Ellen Powell are gratefully acknowledged.

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RHEUMATOID ARTHRITIS:

V. THE AGGLUTINATION OF HEMOLYTIC STREPTOCOCCI*†

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It is well established that the sera of a large proportion of patients with typical rheumatoid (atrophic) arthritis of more than one year's duration possess the ability to agglutinate selected strains of the Group A hemolytic streptococcus to a degree far in excess of normal sera. The reports on this topic have been summarized by Cecil and deGara.² There is general agreement that this ability bears a direct relation to the duration and intensity of the disease.

It is therefore paradoxical that there should exist a large body of evidence against a streptococcal origin for rheumatoid arthritis. This evidence has been summarized¹¹ under three headings: 1. bacteriologic: the repeated failures to recover hemolytic streptococci from the blood of the patients; 2. clinical: the chronicity of the active stage of the disease, its tendency to symmetry, and the ineffectiveness of sulfanilamide and penicillin; and 3. serologic: the absence of antibodies against streptococcal hemolysin and fibrinolysin.

The key to the solution of this dilemma appears to lie in the recent observation¹² that arthritis sera which possess high agglutinin titers are also apt to have the ability to agglutinate suspensions of fine collodion particles, even though the particles have not been sensitized by exposure to an antigen. This phenomenon is probably a non-specific flocculation analogous to such reactions as the Takata-Ara and cephalin-cholesterol. It appears to be related to the non-specific serologic enhancing property which enables rheumatoid arthritis serum to exaggerate the action of normally present precipitins for pneumococcus¹³ and streptococcus¹⁴ fractions

and normally present agglutinins for the non-encapsulated pneumococcus.¹³ The purpose of the present paper is to suggest that the same mechanism is responsible for the potency of rheumatoid arthritis sera in agglutinating hemolytic streptococci.

Aside from any non-specific flocculating power of the serum, two factors exert an influence upon a reaction of this sort, namely 1. the inherent tendency of the test-suspension to agglutinate and 2. the presence in the serum of antibodies which would specifically initiate agglutination. Both factors play a part in the agglutination of hemolytic streptococci by the serum of rheumatoid arthritis.

1. In the recorded observations of streptococcus agglutination by arthritis serum most of the strains of bacteria which have been used have been selected for their agglutinability. A few favorite strains, lent by one laboratory to another, have reappeared frequently in the reports of different observers. Strains selected at random have often been unsatisfactory. It must be pointed out, however, that the question of individual strain-agglutinability has no important bearing on the specificity or non-specificity of agglutination.

2. There are indications that the sera of many normal individuals contain some antibodies directed against hemolytic streptococci of Group A. Precipitins for crude extracts of organisms of this group (a less sensitive test than agglutination of the intact organisms) have been reported^{9,15} in the sera of about 25% of persons who have neither rheumatoid arthritis nor a recent hemolytic strepto-

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coccus infection. The existence of these precipitins has been attributed¹⁴ to the function of the normal human nasopharynx as a natural reservoir for Group A streptococci. Streptococcus agglutinins of weak to moderate strength have been found in the sera of normal people^{3,6,10} and of patients with a wide variety of diagnoses other than rheumatoid arthritis or streptococcal infection.⁵ The incidence and strength of these antibodies led Dawson, Olmstead and Boots⁵ to postulate a final serum dilution of 1:160 as the lowest acceptable as significant in the interpretation of results with arthritis serum. By their criteria a titer of 1:20 or less is "negative," 1:40 or 1:80 "doubtful" and 1:160 or higher "positive." A final serum dilution of 1:20 has been the lowest used by most observers. The use of lower dilutions would presumably reveal the existence of agglutinins in a still higher percentage of normal persons.

Proof that rheumatoid arthritis is not accompanied by a genuine excess of hemolytic streptococcus agglutinins would be difficult because it would be the proof of a negative. The experimental observations which follow are recorded for the sake of helping to clarify the relationship between the streptococcus-agglutinating and the collodion-agglutinating abilities of rheumatoid arthritis serum.

Experimental. In our experience, successive batches of collodion particles prepared by the method of Cannon and Marshall,¹ are apt to vary in stability and agglutinability. In final serum dilutions starting at 1:20, most normal sera gave no agglutination of the collodion particle suspension. In fact, the suspensions were more stable with normal serum than with physiologic salt solution. Infrequently a "normal" human serum was encountered with a titer of 1:20. Controlling each batch of particles with normal human serum and with potent arthritis serum, we have found that agglutination of collodion particles is not produced by scarlet fever convalescent serum (Group A hemolytic streptococcus agglutinin titer, against strain NY5, 1:320) or by rabbit antiserum

(Lederle) aroused by immunization with intact Group A hemolytic streptococci (streptococcus agglutinin titer, 1:640). This indicates that the agglutination of collodion particles by rheumatoid arthritis serum is not accomplished by *specific* action of antistreptococcal antibodies. The lack of correlation between these two agglutinating properties in individual arthritis sera has been previously reported.¹²

Furthermore, preliminary complete exhaustion of hemolytic streptococcus agglutinins in an arthritis serum by absorption with the intact organism usually reduced but did not abolish the ability of the serum to agglutinate collodion particles. In a typical experiment, an absorbed arthritis serum had a collodion titer of 1:40 while an unabsorbed aliquot simultaneously had a titer of 1:320. We interpret this to mean that a portion of the collodion-agglutinating factor was non-specifically adsorbed out during the streptococcus agglutination. (Reversing this procedure, preliminary adsorption with collodion particles decreased the hemolytic streptococcus agglutinin titer of an arthritis serum from 1:640 to 1:160.)

Preliminary absorption with non-encapsulated pneumococcus (strain I-192-R), *Staph. albus* or *Strep. viridans* likewise tended, though not as consistently, to decrease the ability of arthritis serum to agglutinate collodion particles. The greater potency of the hemolytic streptococcus strain (NY5) as a non-specific adsorbent is presumably related to its notorious agglutinability.

Discussion. We visualize the relation between the ability of an arthritis serum to agglutinate: *a*, hemolytic streptococci of Group A; and *b*, collodion particles as follows. The former ability depends on how long and how recently the patient has harbored Group A streptococci; the latter depends chiefly upon the severity and duration of his arthritis. Either, therefore, could exist without the other. When both are present, either will enhance the action of the other, but the enhancing effect of the latter on the former is presumably stronger than the reverse, because

the enhancements are apparently non-specific and the fraction responsible for collo-dion agglutination appears to exceed quantitatively the streptococcus agglutinins.

Most of the reported observations on the agglutination of hemolytic streptococci by rheumatoid arthritis sera have been made with organisms of Group A. Using organisms of Groups B through G, Dawson and Olmstead⁴ found that "significant" agglutination was infrequent, according to their criterion that a titer of 1:160 is the minimal "positive," with the proviso that agglutination must be stronger in the lower than in the higher dilutions. They observed further that "control sera from a variety of diseases agglutinated organisms other than those of Group A to approximately the same degree as did rheumatoid arthritis sera," and concluded that the "agglutination reaction in rheumatoid arthritis sera is one which is highly characteristic of Group A hemolytic streptococci." This conclusion can be reconciled with our thesis that streptococcus agglutination by arthritis serum is explicable as an exaggeration of the action of normally present antibodies by pointing out, as was done¹⁴ in the case of streptococcal precipitins, that among hemolytic streptococci, those of Group A are by far the commonest inhabitants of the normal human nasopharynx.

In a previous paper¹² it has been noted that the collo-dion-agglutinating factor in

rheumatoid arthritis serum, which is apparently related to the non-specific serologic enhancing power of the serum, resides in the globulin fraction and that hyperglobulinemia is characteristic of rheumatoid arthritis. The relationship between altered serum proteins and non-specific phenomena analogous to collo-dion-particle agglutination is well established. An elevated serum globulin (or more accurately, a reversal of the albumin-globulin ratio) has been found responsible for the colloidal gold,⁸ Takata-Ara,⁷ cephalin-cholesterol⁸ and formolgel¹⁵ reactions.

Summary. The occurrence of relatively feeble agglutinins for the Group A hemolytic streptococcus in the sera of normal individuals is attributed to the function of the normal human nasopharynx as a natural reservoir for this organism. In the presence of rheumatoid arthritis, the action of these antibodies appears to be enhanced, in a non-specific manner, by a peculiar property of the serum. This property is apparently related to the ability of arthritis serum to agglutinate suspensions of fine collo-dion particles.

Conclusion. The weight of evidence indicates that the increased ability of the sera of patients with typical rheumatoid (atrophic) arthritis to agglutinate selected strains of hemolytic streptococcus of Group A is due to a non-specific enhancement of the action of normally present agglutinins.

This work was begun in the Laboratory of the Chestnut Hill Hospital, Philadelphia, under a grant from the Charlotte Drake Cardeza Foundation of the Jefferson Medical College. Our thanks are due to Dr. Thomas Cope, Jr., Director of that laboratory, for his cooperation and to Mrs. Charlotte Sommer for technical assistance. The work was completed at the University of Pennsylvania, under a grant from the National Foundation for Infantile Paralysis, Inc. The use of the facilities of the Harrison Department of Surgical Research and the technical assistance of Mrs. Ellen Powell are gratefully acknowledged.

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PROGRESS OF MEDICAL SCIENCE MEDICINE

UNDER THE CHARGE OF

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THE DIAGNOSIS OF PULMONARY DISEASE

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DURING the past decade or so unusually encouraging progress has been made in the surgical and medical management of acute and chronic pulmonary disease. Through an intelligent and prompt utilization of new and perfected therapeutic techniques and measures we are now able to offer a favorable prognosis for survival and hope for cure in many pulmonary diseases which were previously considered inevitably fatal or doomed a patient to chronic invalidism and eventual death. Unwarranted delay, unfortunately, or actual failure to establish the correct diagnosis have only too often deprived many patients of the benefits of successful therapeutic intervention in pulmonary conditions which are amenable to existing and available remedial measures. On occasion, the most astute clinicians are unable to solve some of the more difficult diagnostic problems even after careful and prolonged competent study. This situation is to be expected and excused, but there is no apology for ignorance or failure to utilize all existing and available clinical and laboratory diagnostic aids in conducting an investigation of a pulmonary disease process. It is the purpose of this manuscript to catalogue and discuss

briefly those clinical and laboratory procedures which, if applied intelligently, will help establish accurately and without undue delay the correct diagnosis in conditions involving the lungs. No real effort will be made to evaluate the relative importance of the various procedures mentioned below, as it is felt that the real value of each depends upon its timely utilization and correct interpretation in the light of all other available facts in each individual case.

I. History and Physical Examination.
A. ROUTINE HISTORY. (1) chief complaint; (2) history of present illness; (3) system review; (4) past history; (5) family history; (6) marital history; (7) social history. Logical investigation of each case should begin with a brief clear statement of the patient's chief complaint followed by a detailed and accurate history obtained in a friendly and leisurely manner in the sequence outlined above. The final recorded story of the illness should be an integrated simple word picture of the information supplied spontaneously by the patient to which has been added the examiner's objective observations. Each symptom requires careful evaluation, but the differential characteristics of

those which are especially referable to the lungs deserve painstaking study and correlated interpretation. Particular emphasis should be placed on such symptoms and observations as cough, sputum, hemoptysis, dyspnea, orthopnea, wheezing, cyanosis, pain in the chest, hoarseness, fever, chills, loss of weight, nature of onset and progress of the illness, seasonal, diurnal, climatic and geographic variations, relation to previous illness, and method of obtaining relief. Any or all of these symptoms and observations when present require careful quantitative and qualitative evaluation of their characteristics so that to each may be assigned its rightful significance in the over-all clinical picture.

For example, the symptom cough, unless analyzed carefully and its special characteristics assessed properly, will have no significant value in helping to establish a correct diagnosis. On the other hand, if the differential characteristics of each symptom and observation are evaluated with diligence, the correct diagnosis is suspected or established in many instances while the integrated history of the present illness is being recorded. The history of the present illness should not be recorded in final form until the physician has conducted a detailed system review. This procedure affords an opportunity for the examiner to ask questions which may unearth additional pertinent facts for incorporation in the history of the present illness, or to reemphasize the true significance of previously obtained information. The patient's negative or affirmative reply to a simple routine question in the system review, which on the surface seems entirely unrelated to the respiratory organs, may frequently supply the missing link in a difficult diagnostic problem.

All too frequently the existence of acute or chronic pulmonary disease masquerades behind a curtain of such bizarre symptomatology that even the most experienced examiner is often misled and completely ignorant of the true nature of the disease after the history of the present illness and system review have been carefully ob-

tained. In these instances the true nature of the disease process may be clarified or suspected while obtaining the past history of the patient. Pulmonary tuberculosis, bronchiectasis, and other chronic pulmonary diseases such as fungus infections may be suggested by a past history of recurrent pleurisy, frequent colds and influenza, recurrent and frequent pneumonia with atypical courses, periodic loss of weight and energy without obvious reasons, and recurrent bouts of fever and night sweats of undetermined origin. A recent history of an operative procedure such as a tonsillectomy or tooth extraction, or any localized or generalized infection of the mouth, tonsils, nasal and oral pharynx may focus attention on the possibility of a lung abscess, while a history of amebic dysentery in the past may actually suggest the etiologic agent responsible for the pulmonary lesion. Pulmonary embolism, infarction and metastatic abscesses may be suspected if the examiner obtains a history of phlebotrombosis, thrombophlebitis, recent fracture, or severe localized or generalized systemic infection. The history of a childhood illness complicated in its convalescent stage by pneumonia or a prolonged cough should invite the consideration of bronchiectasis as the diagnosis. Pulmonary abscess, bronchiectasis, and chronic pneumonitis should be considered when one elicits a history of esophageal stricture, carcinoma or cardiospasm. The history of the prolonged use of oily nose drops and oily cathartics requires the inclusion of lipoid pneumonia in the differential diagnosis. Recent intense radiation therapy of a lesion in the region of the thorax should lead one to suspect radiation pneumonitis.^{12 23 25 44} This complication is especially frequent following Roentgen ray therapy for carcinoma of the breast. These are but a few examples of the obvious value of a carefully obtained past history.

The strictly personal elements in a patient's history frequently acquire added significance when interpreted in the light of the family and marital history. This

is especially true of contagious diseases such as pneumonia and tuberculosis or when a hereditary tendency is uncovered to support the possible diagnosis of asthma or cancer. In obtaining the family history the examiner should not accept unequivocally the patient's proffered diagnosis of familial illnesses. He should attempt to confirm all diagnoses supplied by the patient, especially those which may influence the ultimate decision in the case. This objective may be attained by ascertaining and evaluating the signs and symptoms personally or by obtaining the information directly from the physician who established the diagnosis in question. Unless extreme caution is exercised in this respect, many serious errors will be committed in the name of good medicine. Investigation of every diagnosis in this fashion will prove many to be misleading and still others to be completely erroneous. On the other hand, patients will conceal well-established and unquestionable diagnoses in order to avoid what they consider a social onus. This vexing problem is especially true of pulmonary tuberculosis.

Finally, the examiner should obtain the patient's social history. Such pulmonary diseases as silicosis, asbestosis, byssinosis, anthracosis, bagassosis and arc-welder's disease may be suspected from the patient's occupation. Geographic considerations may necessitate the inclusion of coccidioidomycosis, echinococcal disease and other conditions in the differential diagnosis. Psittacosis should be included in the differential diagnosis of patients exposed to members of the parrot family, pigeons and fowl known to harbor the responsible virus. In general, all personal habits which may be of significance in the final analysis of the case should be noted carefully.

An orderly correlated history obtained in this fashion will suggest the diagnosis in many instances before the physical examination or any other procedures are completed. In a substantial number of cases, however, the examiner will be distressed at the apparent lack of assistance

gained from even the most assiduously recorded history. No matter how often this unfortunate situation occurs, the physician must never consciously lower the recognized standards of a satisfactory history. As it so often happens, the first manifestation of carelessness will be rewarded by a missed diagnosis. Those of us who have experienced this pitfall in the past will never again be satisfied with an abbreviated record of a patient's illness. The apparent bonanzas of short cuts to diagnoses have a notorious habit of back-firing at the wrong time to the complete embarrassment of their would-be beneficiaries and to the detriment of the unfortunate guinea pig patient. This latter observation applies with equal significance to all elements of the patient's examination; history, physical and laboratory. The physician, not the clerical helper or nurse, should obtain the history.

B. PHYSICAL EXAMINATION. A routine physical examination of the patient suspected of suffering from pulmonary disease must be performed in each case. No matter how incontrovertibly the evidence in the patient's history points to a pulmonary disease, omission of the slightest detail in the routine physical examination is fraught with danger. In general, the physical findings will confirm or disprove the impressions gained from the patient's clinical history. Quite often a routine examination will reveal significant physical findings in an organ, or organs, other than the one to which the history has directed the examiner's attention. Imagine the physician's surprise when a disease process is located in the left lower lobe of the lung of a patient complaining of anorexia, nausea, vomiting, and epigastric pain. In this, and similar circumstances, the examiner will find it necessary to supplement the original history with new and added information obtained by re-interrogation of the patient for the purpose of emphasizing symptoms referable to the organ involved. It is agreed that a majority of diseases involving the lungs are usually localized processes, but a sig-

nificant minority are merely reflections in that organ of a more remote or systemic disorder. This very fact again emphasizes the necessity of a complete physical examination even in those instances that on the surface do not seem to warrant such a detailed procedure. The discovery of phlebothrombosis or thrombophlebitis in an extremity will not only help establish a more accurate etiologic background for pulmonary embolism and infarction but will also facilitate the institution of prophylactic measures to avoid further possibly fatal accidents. Dependent edema, venous engorgement, and a tender hepatic enlargement will incriminate the heart as the responsible organ rather than the lungs in a patient complaining of cough, blood-tinged sputum and dyspnea. The physical examination in such instances serves to evaluate and correlate the clinical history. A distant lymph node, a draining sinus, a skin lesion, or an enlarged prostate discovered by careful physical examination may reveal the true nature of the pulmonary disease process when examined histopathologically or bacteriologically at the proper time. Such a simple observation as clubbing of the fingers and toes may lead to a suspicion, and subsequent confirmation, of pulmonary disease. It is fairly obvious from these foregoing remarks that a careful complete physical examination, not only of the lungs but of the entire body, is very important in confirming or disproving the existence of pulmonary disease and, on occasion, will reveal a previously unsuspected pulmonary lesion.

II. Clinical and Laboratory Aids in the Diagnosis of Pulmonary Disease. When the history and physical examination are complete and correlated, the diagnosis is often apparent. There are, however, a significant number of pulmonary diseases which can be diagnosed only with the assistance of routine and highly specialized clinical and laboratory diagnostic procedures. Familiarity with all of these procedures, nevertheless, is not only an essential part of the armamentarium of

those physicians who are interested especially in diseases of the chest, but should be equally familiar to all engaged in the practice of medicine and its various specialties. A working knowledge of these procedures will enable the physician to diagnose pulmonary diseases with greater frequency, rapidity and accuracy. In addition, a realization of his own limitations will prompt him to offer the patient the benefit of more specialized consultation study if indicated. In general, all of the following diagnostic measures should be considered as secondary aids and utilized only after a complete history has been obtained and a thorough physical examination has been performed.

A. HEMATOLOGIC STUDIES. It is a rather infrequent occurrence for routine hematologic studies to be of any significant value in establishing the diagnosis of pulmonary disease. A normal red blood count, or one manifesting some degree of anemia is of no particular importance. Both conditions may be found in innumerable pulmonary diseases. Polycythemia, on the other hand, may be a very significant laboratory finding. Its existence may not only help to confirm the diagnosis, but, on occasion, may call attention to underlying pulmonary disease which was not suspected before examination of the blood. Erythrocytosis, when associated with pulmonary disease, usually signifies chronic oxygen lack and may accompany such clinical entities as Ayerza's disease, emphysema, far-advanced cystic disease, or any other condition interfering with adequate oxygenation of the red cells.¹⁵ It is a rather constant finding in pulmonary hemangioma (arteriovenous fistula).^{19,23,25} Erythremia or polycythemia vera is commonly accompanied by pulmonary signs and symptoms.¹⁵ The total white blood count and differential are useful in determining the existence and type of infection. For example, one may usually expect a normal total white blood count with primary atypical pneumonia of undetermined etiology; on the other hand, a definite leuko-

cytosis with a left shift is rather typical of lobar or bronchopneumonia.^{9,24,29,36,42,46} As a rule, however, the total white blood count and differential contribute only limited assistance in helping to establish specific diagnoses in pulmonary disease. It is true, nevertheless, that the finding of an eosinophilia may be the first clue to the correct diagnosis in such diseases as Loeffler's syndrome, Hodgkin's disease, or echinococcal disease involving the lungs.^{5,25} Some degree of eosinophilia has been reported in silicosis, but the author does not believe that the total white blood count or differential is of particular diagnostic significance in this disease entity or in tuberculosis.²⁰ When leukemic processes involve the pulmonary tissue, the total white blood count and differential may be, and usually are, of concrete assistance. Aside from Hodgkin's disease, a study of the white blood cells does not contribute much to the diagnosis or evaluation of the other lymphomas.²⁵ Although it is true that the routine hematologic study of a patient is not too commonly of any real significance in the ultimate evaluation and diagnosis of pulmonary diseases in general, it should never be omitted because, in many instances, it is not only of real help but is practically diagnostic of certain conditions. Also, it must be remembered that a rising or falling total white blood count and a shifting Schilling count have the same prognostic value in pulmonary infections as they do in other infectious diseases.

B. EXAMINATION OF THE URINE. Although the author does not recall any instances of pulmonary disease in which this examination was diagnostic, it should, nevertheless, continue to be a routine laboratory procedure because of its value in considering the differential diagnosis. In acute and chronic pulmonary diseases the urine could conceivably show some secondary changes to which none but the usual significance can be attached.

C. STOOL EXAMINATION FOR PARASITES. In Loeffler's syndrome, the discovery of *Strongyloides stercoralis*, *Ascaris lumbricoides*, *Necator americanus*, or other ova in the stool is of great assistance. When *Endamæba histolytica* cysts or trophozoites are found in the feces, the etiology of a lung abscess may be suspected and subsequently proved. These are but a few examples in which examination of the stool for parasites may yield important diagnostic information.

D. SEROLOGIC TEST FOR SYPHILIS. Only on rare occasions is this test of any diagnostic significance in pulmonary disease. It should, nevertheless, continue to be a routine procedure in the examination of all patients.

E. SPUTUM EXAMINATION. This is one of the most reliable and important procedures and should be utilized routinely in every case of suspected or undiagnosed pulmonary disease. Suitable specimens for examination may be obtained from ordinary expectorated material. When the amount of sputum raised is insufficient or unsatisfactory, material for examination may be obtained by pulmonary lavage or bronchoscopic aspiration of the trachea and accessible bronchi.^{10,11,18} Frequent microscopic examination of appropriately stained smears should be performed in a search for the responsible pathogen. One should not be content with 1, 2, or even 3 negative results if strong clinical evidence exists which incriminates the lungs and points to a certain disease process. Repeated careful examinations are mandatory when tuberculosis is suspected. A concentrated 24 hour sputum specimen is the procedure of choice. The type of stain employed is a matter of individual preference. If the usual staining technique does not yield the desired or satisfactory result, then the sputum should be cultured on appropriate media. Fresh unstained material should be examined when attempting to identify the trophozoites of *E. histolytica*. An unstained specimen mixed with either a 10% solution of potassium hydroxide or sodium hydroxide is also the procedure of choice when a fungus is being sought.^{8,47} When echinococcal disease of the lungs is sus-

pected, the diagnosis may be established by identification of the hooklets or membrane of the cyst in a properly stained specimen.⁵ In all cases of lobar or bronchopneumonia the sputum should be typed in order to identify the specific microorganism responsible for the infection.

If examination of the sputum should end with a search for the responsible pathogenic microorganism, it would be incomplete because the gross and other stained and unstained microscopic characteristics of the pulmonary excreta must be studied in order to secure the maximum diagnostic benefits from this examination. The identification of fat globules will in itself confirm or suggest the diagnosis of lipoid pneumonia. Loeffler's syndrome or asthma may be suspected when the predominating cellular elements are eosinophils, while the additional presence of elastic fibrils and Chareot-Leyden crystals make the latter possibility more probable. The recognition of larvæ of *A. lumbricoides* should suggest immediately an ascariasis pneumonia. If bronchogenic carcinoma is suspected, properly prepared specimens should be examined for cancer cells.^{2,16}

The gross characteristics of the sputum must be studied carefully as this part of the examination frequently suggests the diagnosis. For example, a frothy, rust-colored sputum, with or without blood-streaking, invites a diagnosis of pulmonary edema, while a 3-layered sputum is suggestive of bronchiectasis. Pulmonary tuberculosis, bronchiectasis and neoplasm are among the diagnoses to be considered in the presence of varying degrees of hemoptysis. A very foul-smelling sputum should make one suspect lung abscess or bronchiectasis. Prune juice colored expectoration may signify lobar pneumonia, while anebic abscess of the lung may be characterized by an anchovy sauce colored type of sputum. When the gross characteristics of the sputum are similar to fluid obtained by thoracentesis, a bronchopleural fistula must be considered. The accidental discovery of a broncholith may be the answer to a difficult diagnostic

problem. Characteristic sulphur granules mean actinomycosis until proved otherwise, while the presence of Curschmann's spirals and Laennee's pearls are suggestive of asthma. From the above remarks one should be able to appreciate the value of a carefully performed sputum examination and assign to it a high priority rating on the list of routine diagnostic procedures.

F. GASTRIC CONTENTS. The examination of fasting gastric contents in the aged, the debilitated, and young children may help prove the diagnosis of pulmonary tuberculosis.^{17,37,39} It is frequently the only method of establishing the diagnosis beyond question. This very reliable and valuable procedure should be employed whenever the bacteriologic results of sputum examination by stain and culture are consistently negative while all available clinical evidence, nevertheless, is to the contrary.

G. BLOOD CULTURES. Early in the course of lobar or bronchopneumonia, and before a chemotherapeutic or antibiotic agent has been employed, the blood culture may be positive. Isolation of the responsible organism in the blood stream is not used to establish a diagnosis, but rather to confirm it. As a rule, blood cultures are of very limited value in the diagnosis of pulmonary disease.

H. SKIN TESTS. In many obscure pulmonary conditions the diagnosis may be suggested by an allergic response of the host to a measured minute skin test dose of antigen obtained from a specific microorganism. This test is especially valuable in such diseases as tuberculosis, coccidioidomycosis, blastomycosis, histoplasmosis and other fungus diseases.^{3,7,8,20,41,42} In some instances, a negative result, however, is of far more clinical significance than a positive reaction.³ Physicians should not employ this diagnostic procedure unless they are thoroughly familiar with the correct technique of performing the test and how to read and interpret its results. When echinococcal disease of the lungs is suspected, Casoni's intradermal test is practically specific.³ All asthmal-

tics should be tested for allergic response to suspicious antigens both for diagnostic purposes and therapeutic possibilities.

I. SEDIMENTATION RATE. For many years this determination has been a practically routine procedure in the study of some chronic pulmonary diseases. Its popularity certainly does not originate from its diagnostic value, but may be attributed to its questionable prognostic significance and ease of accomplishment. It is a non-specific laboratory test which should be interpreted and accepted only in the light of the over-all clinical and laboratory picture.

J. PRECIPITIN AND COMPLEMENT-FIXATION TESTS. These procedures are of real value in the diagnosis of virus and fungus diseases. When significant positive results are obtained, they may be considered diagnostic. In some instances, as for example in blastomycosis and coccidioidomycosis, a rising or falling of titer is of prognostic as well as diagnostic value.^{8,26,40}

K. ROENTGENOLOGIC EXAMINATION. No examination of the lungs is complete without a Roentgen ray film of the chest. An erect posterior-anterior view should be a routine procedure for all patients suspected of having pulmonary disease. The author shares the opinion that a good lateral view of the chest is as important a routine procedure as a posterior-anterior film.⁴ Not infrequently lesions are recognized on the lateral view which are not even suspected after the most careful interpretation of the posterior-anterior film. If economic considerations permit it, and time, equipment and personnel are available, the lateral view should be a routine procedure in the diagnosis of pulmonary disease. Roentgen ray examination of the lungs is unquestionably one of the most valuable of all diagnostic procedures, but under no circumstances should it be considered a substitute for the routine history and physical examination. The real and full value of a chest Roentgen ray can be realized only if its final interpretation is made contingent on the history, the physical examination, and

other clinical and laboratory procedures. On occasion, the results of physical examination of the lungs are more informative than the roentgenogram. More frequently, however, the Roentgen ray will reveal a pulmonary lesion even after the most competent physical diagnostician has rendered a negative opinion. This unfortunate shortcoming of the physical diagnosis in the recognition of pulmonary disease can be corrected only through increased utilization of routine Roentgen ray examinations of the lungs at regular periodic intervals. Equipment and supplies for mass radiographic campaigns are now becoming increasingly available and the cost is so nominal that even economic considerations are of no real consequence. One should remember, nevertheless, that a Roentgen ray film of the lungs is only infrequently diagnostic of pulmonary disease. It does, however, permit early detection of silent and unsuspected lesions and careful follow-up examinations. Therein lies its greatest contribution to the study of pulmonary disease.

The following Roengen ray studies of the lungs are valuable diagnostic procedures: (1) erect posterior-anterior; (2) lateral; (3) oblique; (4) lordotic; (5) stereoscopic; (6) planographic studies; (7) kymographic studies; (8) bucky film; (9) spot film; (10) maximum inspiration and expiration. Any of these studies, and especially the more difficult technical procedures, should be undertaken and interpreted only by physicians qualified to engage in the practice of roentgenology or diseases of the chest. The adequate study of pulmonary diseases is so dependent on the Roentgen ray examination that it is almost obligatory for phthisiologists and other chest physicians to be competent roentgenologists as far as the thorax is concerned. Each of the examinations mentioned above has a definite place in the study of pulmonary diseases, and, if properly employed at the correct time, will yield gratifying results in the hands of competent individuals. On occasion, a study of any part of the gastro-

intestinal tract with a radiopaque substance such as barium may be indicated because of differential diagnostic considerations. This is especially true in diaphragmatic hernias and diseases of the esophagus. Roentgen ray examinations of other parts of the body may also be indicated under certain circumstances, but the occasions are so inconstant and the variety of examinations so multitudinous that it is merely mentioned in passing for completeness. For example, if the pulmonary lesion appears to be metastatic, one is required to investigate all possible primary sites.

L. FLUOROSCOPY. This study of the lungs is very valuable in determining mobility and other dynamic features of the chest during various phases of respiration. One may study and estimate the functional vital capacity of each lung in this manner by noticing the changes in its density during various respiratory phases together with the movement of the ribs, mediastinal structures, and excursion of the diaphragm. Aneurysms may be diagnosed from their expansile nature and so differentiated from solid tumors. Fluoroscopy is of untold value in such conditions as pneumothorax and pleural effusions. It is no adequate substitute for Roentgen ray photographs of the lungs. Too many lesions escape detection by even the most competent fluoroscopists if sole reliance is placed on this method of examination. However, when it is necessary to consider the gastro-intestinal tract in the differential diagnosis of pulmonary disease, fluoroscopic examination is probably a more important study and reliable evaluation than the roentgenogram.

M. EXAMINATION OF PLEURAL FLUID AND GASES. Whenever the presence of a pleural effusion is ascertained, a specimen must be obtained for diagnostic purposes as soon as possible. Unless specifically indicated, air should not be introduced into the pleural cavity during, or following, diagnostic aspiration. A part of the fluid obtained should be consigned for bacteriologic examination. If the

specific diagnosis is suspected, special stains, cultures and other bacteriologic studies may be carried out. For example, if one suspects a tuberculous effusion, then a guinea pig inoculation is in order. Fluid which has developed synpneumonically, or metapneumonically, should be typed for specific pneumococci. If one suspects a malignancy, part of the specimen should be examined histopathologically for neoplastic elements. The type of leukocyte, if present, can be determined from a stained smear while searching for pathogenic bacteria. In this way the inflammatory nature of an effusion can be detected. Sufficient fluid should be obtained to determine the specific gravity or protein content. These examinations are valuable in differentiating an exudate from a transudate. Before withdrawing the aspirating needle, 10 cc. of 1% methylene blue, or some other suitable dye, may be instilled if a bronchopleural fistula is suspected. In the presence of this complication the sputum will have a bluish discoloration within 12 to 24 hours, or sooner, following injection. This is a very valuable diagnostic aid which offers incontrovertible evidence when positive. Where facilities for gas analysis are available, the existence of a bronchopleural fistula may be suggested by a determination of the carbon dioxide and oxygen content of gas obtained from the pleural cavity.²⁷ This time-consuming procedure is usually unnecessary and merely of academic interest.

Macroscopic examination of the fluid obtained by thoracentesis is not a very reliable procedure; but odor, viscosity and color may suggest certain diagnostic possibilities and methods of examination. For example, a pale straw-colored fluid obtained from the right hemithorax may suggest congestive failure with hydrothorax. Milky, thin fluid invites the diagnosis of chylothorax which can be confirmed by staining with Sudan III and chemical analysis of its fat content.²⁸ A blood-tinged, or frankly bloody, fluid suggests pulmonary infarction, trauma,

congestive heart failure, tuberculosis, pulmonary or pleural neoplasm, and other possibilities. Foul-smelling fluid may suggest an anaërobic infection or a colon bacillus. These gross features should all be evaluated in the light of the available clinical and other laboratory evidence and appropriate further study undertaken to prove the diagnosis. From this brief discussion the diagnostic importance of fluid in the pleural cavity should be obvious, and the physician must be prepared to obtain every possible assistance from the complete investigation of this easily available pathologic material.

N. BRONCHOSCOPY. This diagnostic aid is not employed with sufficient frequency in the diagnosis of pulmonary disease. Yet, it affords the clinician an opportunity to visualize the lesion directly, if it is located in an accessible area, and to obtain material for bacteriologic and histopathologic examination with which to establish the diagnosis. The appearance of some lesions is almost diagnostic. In any unexplained pulmonary disease, or suspected tracheo-bronchial disease, this examination should be performed without procrastination as it is a relatively harmless procedure in the hands of competent bronchoscopists.²¹ The physician should not hesitate to submit his patient to this examination for the expected benefits are far more numerous than the possible dangers. Bronchoscopic examination should be considered in all cases of obscure and atypical pulmonary lesions in all patients past the age of 40. In this way more cases of pulmonary cancer will be discovered in an operable and possibly remedial stage.^{22,30,33}

O. ESOPHAGOSCOPY. On occasion this may be a very valuable procedure in differentiating between esophageal and pulmonary disease. Not infrequently, esophageal disease is discovered to account for secondary pulmonary complications as in stricture and carcinoma of the esophagus or cardiospasm.

P. BRONCHOGRAPHY. The introduction of a radiopaque substance (lipiodol) into the tracheo-bronchial tree is a simple, safe

and valuable procedure. It is of unparalleled value in cases suspected of having bronchiectasis and may also be employed to demonstrate bronchial occlusions, cystic disease and pulmonary cavitation. The method of choice in carrying out this examination is one of individual preference. Following the instillation of lipiodol into the tracheo-bronchial tree, immediate fluoroscopic and photographic examination should be performed.

Q. MISCELLANEOUS USES OF RADIOPAQUE MATERIAL. When a sinus tract appears to communicate with the lung or the pleural cavity, lipiodol, or some other suitable material, may be used to outline the tract and to ascertain the communication. In positive instances the lipiodol can be demonstrated in the lungs fluoroscopically and roentgenologically. This procedure may be especially useful in thoraco-abdominal actinomyces with sinus tracts.

R. BIOPSY OF LESION FOR HISTOPATHOLOGIC AND BACTERIOLOGIC STUDY. When a diagnosis cannot be established by sputum examinations or other simple laboratory techniques, biopsy of available pathologic material may be performed. The tissue should then be examined by the proper histopathologic and bacteriologic methods.

Material for biopsy may be obtained from the local pulmonic lesion or from other sites if the pulmonary disease process is part of a general systemic condition. Suitable specimens may be obtained bronchoscopically if sufficient material is biopsied from the proper portion of the lesion.^{22,30,33} Bronchial adenomas have a tendency to bleed following biopsy, but this is only a minor complication and should not be considered a contraindication to the procedure. The bronchoscopist must be well oriented before securing the biopsy specimen and is required to determine carefully before the operative procedure is undertaken the possible existence of a thoracic aneurysm. Accidental biopsy of the aorta or other great vessels may be a rather embarrassing complication. When

material for biopsy has been found inaccessible bronchoscopically, the author has unhesitatingly performed innumerable punch biopsies of pulmonary lesions situated at respectable distances from vital structures. If a Vim-Silverman biopsy needle is used, sufficient material of diagnostic quality can be obtained without any more serious sequelæ than transient blood-spitting. Aspiration biopsy is not as satisfactory as material obtained in this fashion is usually insufficient for adequate histopathologic examination, although quite frequently suitable for bacteriologic study. When pulmonary tissue is not available for histopathologic, or bacteriologic, examination or has been found non-diagnostic, material may be obtained from other accessible sites. In such instances one may ascertain the diagnosis from an involved lymph node, a skin lesion, a draining sinus, or from any other site involved by the same disease process. If it appears that the pulmonary disease represents a metastatic lesion, then, in any event, biopsy of the original focus is preferable. Suspected leukemic infiltrations of the lung may be diagnosed by aspiration or biopsy of the sternal bone marrow. Histopathologic and bacteriologic examination of involved tissue obtained by biopsy is an excellent and usually safe method of establishing an etiologic diagnosis quickly and indisputably.

S. DIAGNOSTIC PNEUMOTHORAX. This is a very excellent method of distinguishing between intrapulmonary and extrapulmonary lesions.

T. DIAGNOSTIC PNEUMOPERITONEUM. This procedure has very little place in the diagnosis of pulmonary disease unless diagnostic pneumothorax fails to reveal the exact location of a lesion in the region of the diaphragm.

U. THORACOSCOPIC EXAMINATION. After a diagnostic pneumothorax of sufficient quantity has been induced, it is a relatively minor surgical procedure to examine the contents of the pleural cavity

with the thoracoscope. This sometimes permits direct visualization of the lesion for purposes of surgical evaluation and diagnosis. Biopsy specimens may be obtained in this manner for histopathologic and bacteriologic examination.

V. THE ELECTROCARDIOGRAM. This procedure has very limited value in diagnosing pulmonary lesions. As in the case of cor pulmonale, it frequently reflects cardiac and pericardial complications and effects of pulmonary disease, but, if the investigation has been conducted correctly and in logical order, the information obtained from the electrocardiogram will be of confirmatory rather than diagnostic importance. When the differential diagnosis rests between pulmonary embolism and coronary occlusion, however, it may be of real diagnostic value.¹ Low voltage in the presence of massive pleural effusion is only of academic interest.

W. VENOUS PRESSURE AND CIRCULATION TIME. In the presence of cardiac failure the venous pressure is commonly elevated. This is not usually the case in pulmonary disease. On occasion, primary or metastatic tumors in the thorax will obstruct the venous return from one part of the body or another, but this is rarely symmetrical as one would expect in cardiac decompensation. This latter observation together with other available evidence, such as collateral circulation, will usually decide the issue.

Determination of the circulation time in pulmonary disease is of questionable value although it is significantly prolonged in many cases of anthracosilicosis.⁴ A prolonged circulation time is a far more constant characteristic of cardiac decompensation than pulmonary disease. The venous pressure and circulation time are of definite value in helping to differentiate between cardiac and pulmonary disease processes.

X. THERAPEUTIC TEST DOSE OF DEEP ROENTGEN RAY THERAPY. If a pulmonary lesion remains undiagnosed after all available diagnostic procedures have been

utilized, then a test dose of deep Roentgen ray therapy is indicated. Response to this form of therapy is very striking in lymphoblastomas and its successful utilization is both therapeutic and diagnostic.^{13,45}

Y. ANGIOCARDIOGRAPHY. An intravenous or intracardiac injection of a radio-paque substance will frequently differentiate vascular tumors of the thorax from other pulmonary lesions.^{14,41} The diagnosis of pulmonary arteriovenous fistula can be established beyond question by correct utilization of this procedure. This diagnostic procedure is not without danger and requires highly trained technical assistance and rather involved apparatus.^{14,23} It is, therefore, not recommended as a routine procedure.

Z. EXPLORATORY THORACOTOMY. If all other examinations fail to establish the diagnosis, the physician is justified in recommending this diagnostic procedure as the last resort in certain selected cases. In the hands of a competent thoracic surgeon this procedure carries no greater risk than an exploratory laparotomy and may eventuate in a cure.

Some pulmonary diseases may be encountered which will require the supplementary utilization of other indicated and highly specialized procedures in order to establish the correct diagnosis. For example, bronchspirometric studies, gastroscopic examination, determination of the alkaline phosphatase blood level, or a retrograde pyclogram may be necessary to establish the diagnosis in some instances. To enumerate and discuss all these possibilities would be an almost impossible assignment. As a rule, intelligent utilization, correct interpretation and careful selection of indicated clinical and laboratory procedures enumerated above will be rewarded by a prompt and accurate diagnosis of existing pulmonary disease.

In recent years there has been a perceptible and annoying tendency among some physicians to discredit the value of the history and physical examination of a

patient suspected of having a pulmonary disease and to place greater and almost complete reliance on laboratory methods of diagnosis. This practice has reached the point where only the more fortunate patients receive the benefit of even a cursory physical examination, and this after they have submitted to all sorts of complicated, expensive and oftentimes superfluous laboratory procedures. In those instances where it is the added practice of the physician to rely on a clerical aid, a technician, or a nurse to obtain the abbreviated form-fitting history, the patient may not even see the doctor except to hear the final expensive verdict of the assembly line boss. Unfortunately, this deplorable trend not only destroys the very valuable personal patient-physician relationship on which the practice of modern medicine is built, but is supplying effective ammunition for the guns of those who are blasting at our present medical structure and demanding socialized medicine.

The foregoing considerations of the manner in which diagnostic clinical and laboratory procedures are employed should not be construed as an effort to minimize the importance of these very valuable and occasionally indispensable aids. On the contrary, it is felt that the correct diagnosis of many obscure pulmonary conditions would be almost impossible, or never established, without readily available facilities for performing these examinations when indicated. After the examiner has obtained the history and conducted the physical examination, in the manner previously outlined, the selection of possibly beneficial diagnostic procedures is the next logical and important step in the diagnosis of pulmonary disease. Investigation of the illness in this scientific manner and orderly sequence will result in a much higher incidence of prompt and correct diagnoses. The patient and physician will both benefit from this approach to the problem. Fewer laboratory procedures will be performed and more diag-

noses will be made. To render a patient the best possible service, the physician must be thoroughly familiar with and willing to practice the proper and acceptable methods of orderly investigation.

Summary. 1. The importance of a prompt and correct diagnosis of pulmonary disease has been emphasized.

2. An orderly and scientific manner of investigation has been outlined.

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NEUROLOGY AND PSYCHIATRY

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PERSONALITY REPERCUSSIONS OF ANTERIOR POLIOMYELITIS

A REVIEW OF THE LITERATURE

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ANTERIOR poliomyelitis has rightfully come into the limelight of public attention and scientific inquiry. However, too little consideration has been given the patient as a total personality, often rendered a handicapped individual by the disease. The report, to follow, is a summary of the rather meager literature in English dealing with the repercussions on the total personality wrought by anterior poliomyelitis, both in its acute phase and during subsequent reaction to bodily disfigurement and disability. This résumé of the available literature and unpublished data related to that aspect of the disease is tendered in the hope that greater emphasis will be focussed in the future upon the patient as a total functioning unit, as research progresses toward defining the cause and cure of the disease—and the more effective rehabilitation of its victims.

Considerably more has been written and described about constitutional and neuropathic predispositions to the disease than about its long-term effect on personality functioning and readjustment capacities. Draper⁶ (1932) reemphasized his delineation of what has been called a "poliomyelitic type," and quoted from his book (published in 1917) his description: "The type of child which seems most susceptible to the disease is the large, well-grown, plump individual who has certain definite characteristics of face and jaws; is broad

browed, and broad and round of face. . . . The wide spaced dentition has been a striking feature. . . .

". . . Among the adolescents and young adults who acquired poliomyelitis . . . usually fatal, the type differed from that which is described. Instead of the very large, well nourished individuals with widely spaced teeth, there appeared a delicately made type. . . ."

To this description in 1917, the author added in 1932: ". . . It appears that the constitutional structure of the infantile paralysis people points toward deficiencies of 3 glands, namely: pituitary, gonad and adrenal cortex." He concluded that "the highly specialized type of child described . . . is a causal factor in the occurrence of infantile paralysis, of equal importance with the virus; but so far as the development of paralysis is concerned, the constitution of the child is of greater significance than the virus."

After observation of 1004 patients or photographs of patients, Aycock¹ (1941) supported Draper's concept and the corresponding clinical impression of a common constitutional factor; *i. e.*, a "poliomyelitis type." He remarked that the frank disease tends to occur in a limited number of the individuals exposed, and that these are individuals "of an autarchologic susceptibility, as shown by the tendency of the disease to familial aggre-

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gation and that the character in question is a physiologic difference of an endocrine nature which, although to a considerable extent subclinical, manifests itself in the clinically discernible characteristics. . . .

It appears, therefore, that the selective character of the disease must be borne in mind in any statistical comparison of post-poliomyelitic patients with "normal" controls. In addition to these constitutionally determined physical predispositions, there may also be constitutional neuropathic and psychopathic determinants. For example, Neustaedter¹¹ (1912) reported that of 25 cases, 19 had hereditary neuropathic constitutions, and added that he believed that this was sufficiently suggestive to warrant further investigation.

While acknowledging the scarcity of reported investigations, there has been little tendency to accept personality disorders as resulting from the poliomyelitic infection. A French writer, Zara¹² (1934), reports what he believed was a likely causal relationship between poliomyelitis acquired in infancy (with severe sequelæ) and schizophrenia developing at 33 years of age. Whether he related the psychosis to the infection or to its sequelæ is not clear from the abstract translation. On the other hand, Gordon *et al.*⁷ (1939) investigated psychometrically 98 poliomyelitic patients and declared: "This study shows that an attack of poliomyelitis does not, either at the time or subsequently, depress the level of general intelligence as estimated upon the Stanford-Binet scale." The authors remarked that long absence from school, or the development of emotional reactions to environment resulting in personality maladjustments may determine definite educational backwardness simulating true mental retardation.

Of some psychobiologic import is the controversial term "mental alienation," stemming from Sister Kenny's concept of infantile paralysis. Describing this factor, Bohnengel¹ (1911) has written: "In addition to being studied as a function of the neuromuscular system, muscular activity should be studied also as a function

of the total organism as embodied in the concept of the personality and its functions." "'Mental alienation,'" he suggested, "is composed of a sensory factor ('loss of mental awareness') and a motor factor ('mental alienation' in its narrower sense). . . . 'Loss of mental awareness' seems to correspond to psychosensory (proprioceptive) dissociation, and 'mental alienation' to psychomotor dissociation." The author then concluded that "this syndrome comprising disturbances in the proprioceptive and motor functions of the personality is not peculiar to infantile paralysis. Rather, it appears to be the psychobiologic reaction to muscular immobilization due to any cause and has as its background not cellular pathology alone but the entire psychobiologic organization of the individual."

Knapp¹⁰ (1944) dissented in this regard, believing that Sister Kenny's term "mental alienation" is "a very unfortunate term because it implies a psychologic cause of loss of function which is not justified by the clinical observations. . . . 'Mental alienation' is probably only a minor factor in infantile paralysis and is probably not psychologic in origin as thought by Miss Kenny."

Elsewhere, Bohnengel¹ (1914) wrote in evaluation of the Kenny concept that "'mental alienation' and 'muscular in-coordination' appeared to be in the nature of psychobiologic reactions to the effect of the disease as well as to certain methods of treatment. Both of these symptoms respond to reeducation which, in large measure, is a psychotherapeutic procedure."

A report on the acute- and after-care of patients in a New York City poliomyelitis epidemic of 1916 was furnished by Grossman⁹ (1917), based upon the program financed by a voluntary "After-care Committee." The report contains no reference to possible personality deviations occurring, nor to any utilization of psychotherapy *per se*. By 1938, however, Griffin *et al.*⁸ were able to report a "strikingly successful" a mental hygiene

program pursued during the acute and early convalescent stages of a Canadian epidemic. During a 1937 epidemic of poliomyelitis, 2635 persons in Ontario were affected and of these "over 1000 sustained paralysis sufficiently severe to warrant orthopedic treatment." Recognizing that unavoidably long convalescent periods would be required, these workers, assisted by the Provincial Department of Health, organized and carried out a mental hygiene program with a staff consisting of neurologist, psychiatrist, psychiatric social worker, 4 occupational therapists, as well as volunteer librarians, teachers, artists and occupational therapy students.

Their report is quoted at some length because it represents apparently the earliest such project of this extent: "Every child more than 4 years old was seen by the psychiatrist or the psychiatric social worker, either during admission or soon afterwards. . . .

"Occasionally children with emotional problems of one kind or another were found. There were several severe cases of homesickness. The commonest psychologic factor here was an abnormally strong attachment to the mother. .

"The difficulty of appraising the results of this mental hygiene program is obvious enough. Mental health and wholesome attitudes are attributes which are not easy to measure quantitatively. By observing the change in the children during their 3 weeks stay, however, and by observing them again on their return to the Hospital for Sick Children for re-examination, the writers were left with little doubt as to the efficacy of the measures employed. They were strikingly successful. . . .

"The program in psychologic medicine introduced into the Ontario Orthopedic Hospital served a twofold purpose. Primarily organized to give the younger patients guidance in adjusting to a prolonged convalescence, the hospital was also used as a demonstration center. . . . The parents of the patients received instruction not only in physical

management of the paralyzed patient, but also suggestions whereby psychologic problems could be anticipated and met."

Ripley *et al.*¹² (1943) analyzed in considerable detail the personality factors in patients with muscular disability (not restricted to the poliomyelitic residuals). They declared: "In the analysis of the personality reactions, the following factors were found to be of more importance in determining the adjustment than was the clinical entity (tabulation is that of present author): (a) The various psychobiologic factors, which aside from the muscular disability, have operated in the formation of the personality make-up; (b) the type of muscular disability (weakness, fatigability or incoördination); (c) the muscles involved, and the physiologic, economic and cosmetic significance of these muscles; (d) the age when the muscular symptoms first appeared; (e) the nature of the onset of symptoms (acute or insidious); (f) the length of time the symptoms have been present; (g) the course of the disability (constant, slowly progressive, rapidly progressive or variable)."

The authors thought of these factors as "environmental stresses requiring new adaptations from a consistently reacting and adjusting organism;" and elaborated: "Muscular disability induces no change in the basic structure of the personality, but accentuates underlying traits which have been determined previously by the constitutional make-up and environmental situation. . . .

". . . In the disability of sudden onset, there is a definite change from the status of muscular function before the disease began. The result is anxiety, which often decreases when the disease becomes chronic, or even disappears if the symptoms become arrested. When the onset is insidious, there is usually a gradual adaptation and a relatively mild emotional reaction to the illness. In this latter group, as long as disability is not marked, changes in routine of life can be made with facility unless marked psychoneurotic personality features have been

present prior to the illness. A transient depression in reaction to the disability is often found, particularly when the individual is unable to carry out some activity at which he had previously been proficient. Compensation for loss of function may be made by the development of personality traits, such as conscientiousness, cautiousness, perseverance or excessive aggressiveness.

" . . . When the patient continues to take an interest in his occupation and other people, he may be diverted to a great extent from his symptoms until the handicap has become so great as to preclude normal activity. Resentment toward the affliction is seen in most patients at one time or another. Frequently, it is transferred to the environment in the form of irritability. . . .

"The part of the body involved was of importance in some patients. In general, the upper extremities were more essential to normal personality function than the lower extremities. The hands offered a more satisfactory means of expression and compensation than did the feet. Sexually, however, the lower extremities took on special significance as essential parts of the sexual equipment, both cosmetically and physiologically . . . In those with narcissistic tendencies there was greater sensitivity to muscular wasting itself, and sometimes a resultant development of anxiety, depression or resentment . . .

"The age of the patient acted as an important factor, in that the psychic trauma was least marked in young patients who were still under the protective care of their parents whether the disease was acute or insidious in onset. The emotional difficulties of the parents frequently were found to be greater than those of the patients themselves. In children the cosmetic factor and the functional inferiority became of major importance as they passed through adolescence into sexual and social maturity. Sensitivity to the defect was developed during this period and set off a series of reactions which led to definite changes in personality."

The validity of these factors in poliomyelitis specifically was borne out statistically by a follow-up study of 100 children recovering from that disease, reported by Copellman⁵ (1944), a medical social worker. This report was based upon social work studies in conjunction with the New Haven Hospital and Clinic after an epidemic in 1943. Among these 100 patients were 7 instances requiring frank psychiatric treatment of either the child (4 cases), or one of the parents (3 cases). The author suggested 3 possible causes of maladjustment: (a) the direct effect of the virus upon behavior; (b) the tendency of the disease to select constitutional inferiors as victims; and (c) (most likely in opinion of that author) the threat of a feared disease, isolation in hospital, separation from parents, strangeness of treatment, long convalescence, and the possibility of chronic paralysis. In the same study 38 of the 100 patients demonstrated "behavior problems" sufficient to induce parents to seek assistance. These seemed to result from the (a) tendency of the experience to precipitate or activate previous conflicts in child or family, and (b) irritability stemming from the long convalescence. Such behavior problems were manifested primarily by refusal to eat, nightmares, enuresis, temper tantrums and especially (in 27 of 38 patients) weeping upon slight provocation. The author concluded: "Study of these children has convinced us that there are manifold problems in the readjustment of the children to home and school after a disease such as poliomyelitis, and that the social worker does have an important function in working with these children and their families until a satisfactory adjustment is made. We are convinced that the convalescent period extends over a period of months, even though the child appears to be completely well, and he should get special consideration from parents and teachers."

Referring to muscular disability in general, Ripley *et al.*¹² (1943) clearly emphasized that: "The recognition of emotional factors is of importance not only in diag-

nosis, but also in treatment. Rapport with an understanding physician can give much comfort to the physically handicapped individual. The physician in whom the patient has developed confidence exerts a powerful suggestive effect by his talk and manner on the ability of the patient to function at his optimal level. In some cases there may be an actual relaxation of muscles so that spasticity is decreased and fatigue lessened, enabling the muscles to work more efficiently. Anxiety, resentment and depression are decreased by allowing the patient to unburden himself to an interested listener. . . . Attention to interpersonal relationships in the home setting makes discussion with other members of the family desirable. This is particularly advisable in the case of children whose parents show anxiety. . . .

"Suggestion played an important part in the symptomatic change after administration of various medications."

It will be noted that these therapeutic measures are uniformly empirical in nature. From a psychiatric standpoint there has been reported no satisfactory investigation of the psychodynamics involved in adjustment of the poliomyelitic patient to long-term convalescence and to more or less permanent deformity and malfunction. In 1941, Billings² (1946) proposed a detailed program for a comprehensive and long-term psychiatric study of selected patients afflicted with anterior poliomyelitis. The war intervened and prevented execution of the study, but in 1946 he revised the program plan for presentation to the National Foundation for Infantile Paralysis by representatives of the University of Colorado School of Medicine and Hospitals¹³ (1946).

In the *interim* between completion of the plan and its presentation to the National Foundation, the psychiatric and psychiatric liaison departments of that university completed an initial study of 11 cases. A preliminary description of the procedure and findings in these 11 cases is contained in the last (unpublished) reference¹³ (1946). The patients incurring

acute anterior poliomyelitis who were above the age of 13 years were selected for study during hospitalization. Each of the 11 cases was investigated by a "standard" history with psychiatric emphasis, thorough physical and neurologic survey, a Rorschach test, social history from near relatives, an electro-encephalogram, and a follow-up thematic apperception test. It was proposed that during convalescence and after discharge from the hospital further follow-up examinations and a repeat Rorschach test be carried out in the case of each patient. Describing initial attitudes toward the disease, it was noted: "Almost all the patients expressed on query a feeling of shock and fear for their lives when they first learned their disease was polio. Most reacted with depression and tearfulness or a desire to tearfulness. Almost everyone felt that most polio patients die or are so severely crippled they are complete invalids for the rest of their lives. It is interesting that the nurse in the group felt similarly although intellectually aware that most polio patients do not die and few are completely incapacitated by residual paralysis."

The report includes a descriptive analysis of the 11 patients with their varying personality deviations and reactions. It was predicted that Rorschach studies may well prove of great interest and importance and that in this series "most records show anxiety and/or neurotic shock." Many manifest somatic concern. One patient reacting to a severe infection with marked depression was subjected to Rorschach tests 5 weeks apart, eliciting the following interpretations: "In the first record taken during the forepart of her illness, we see evidence of a traumatic background and some neurotic tendencies. In addition is a severe reaction to her present situation with the expression of tremendous insecurity and color and shading shock. Depression of affect is apparent as well as severe constriction of emotion and thinking and withdrawal from reality. In a record obtained 5 weeks later there is much improvement, as is shown by the liberation

of fantasy material, rejection of only 1 card, reduction in reaction time, increase in the number of responses, and the appearance of tension material completely blocked by repression in the first record."

This preliminary survey represents a promising approach toward definition of the fundamental dynamics underlying personality deviations in association with the psychic trauma, disorders in personality "effector" functions and situational factors, inherent in (a) anterior poliomyelitis in particular, and (b) chronic debilitating and deforming diseases in general. It would seem that until such investigations are pursued systematically with adequate numbers, controls and periods of observation, psychosomatic and psychiatric management (both prophylac-

tic and corrective) must remain upon an empirical basis.

Summary. The literature and some unpublished data are reviewed in summary with reference to personality deviations occurring with or following infections of anterior poliomyelitis. Systematic investigation of the psychobiologic repercussions from anterior poliomyelitis is particularly needed to evaluate the long-term effects wrought upon the personality by prolonged illness, deformity, loss of function, and resultant disturbance of the body image generally. Information derived from such research, if and when pursued, should enhance immeasurably the efficacy of over-all management of the "polio" patient by disclosing verifiable principles for his psychotherapy to supplant the present empiricism.

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PSYCHOSOMATIC RELATIONSHIPS IN ACUTE ANTERIOR POLIOMYELITIS

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IN the recent primer of poliomyelitis published by the American Orthopedic Association we see an excellent definition of the disease: "Poliomyelitis, or infantile paralysis, is an acute generalized systemic disease caused by a virus and characterized by inflammation of various parts of the central nervous system, but particularly by the damage to or destruction of the large motor cells in the spinal cord, with resultant paralysis of the voluntary muscles innervated by them."¹

The history of poliomyelitis probably extends back into antiquity. On an Egyptian tombstone dating from the 2nd century before Christ, there appears the figure of a man typically crippled by this disease.² In recorded medical history as far back as 1784 we find a description of the disease by Michael Underwood, a British pediatrician. In 1835 John Bodham reported 4 classical cases in children occurring in England. It was Jakob Heine in 1840 who published the first extensive monograph of the disease, describing in detail the features of the disease and a discussion of its treatment. This was followed in 1860 by a second paper in which he pointed out the "spinal" character of the disease. Description and pathology were elaborated by such men as von Reinkes, von Recklinghausen, Rissler and others. In 1890 Medin laid down the foundation of the epidemiology of poliomyelitis in pointing out that the disease was, without doubt, infectious in origin. From his and Heine's work, the name Heine-Medin's disease was derived and applied to this disease. For elaboration of the epidemiology, etiology, pathology and prophylaxis, the reader is referred to the many excellent articles on these features in the current literature, such as

Toomey,¹⁸ Sabin,¹⁶ Faber and Silverberg,⁵ Francis,⁶ and others.

The first epidemic noted in this country was recorded by George Colmer in 1841. Subsequent epidemics have come and gone. This year (1946) has been recorded as the worst poliomyelitis year in 3 decades. This is the 4th successive year in which the polio rate has been very high. It was during the present epidemic that it reached startling proportions in the state of Colorado and our attention was brought to the problem of emotional reactions to this disease. The many requests for psychiatric aid in the treatment of these individuals during the acute and convalescent period emphasized the need for a study of the emotional impact of this disease on the personality. The need to study the patient from a psychosomatic standpoint, to study the patient as a whole, rather than the disease alone, was apparent. We have searched the literature for a report of such a study but have found only signposts in various papers indicating the need for a psychosomatic study of poliomyelitis. Many papers comment in a general way: "The attitude of the patient and the family toward the wearing of the splint depends on whether it is worn and may be a deciding factor in determining success or failure of the treatment" (Stevenson¹⁷). "The child crippled by poliomyelitis may, unless care is taken, develop emotional reactions to his environment which may result in serious personality maladjustment" (Gordon⁷). "Remote sequelæ of a psychasthenic or neurasthenic nature were more common than previously noted. Insomnia and nightmares were complained of. Irritability and emotional instability were noted and some complained of mental

fatigability with poor power of concentration, all of which might be indicative of a mild cerebral involvement. Neurocirculatory asthenia was common, the sudden weakness, vertigo, palpitation and breathlessness probably being due to sudden lowering of vascular tension incident to sympathetic dysfunction" (Bower,³ and others^{13,15}).

In the recent primer of poliomyelitis of the American Orthopedic Association,¹¹ it is pointed out that the emotional and psychologic manifestations in poliomyelitis have not been adequately studied or evaluated. Barbour,¹ in a 4 year follow-up (1935) of the adjustment of 60 handicapped poliomyelitis individuals, reported that 6 (10%) of these 60 patients with residual paralysis showed emotional maladjustment and he pointed out the obvious need for psychiatric help in those disabled. A study by Griffin *et al.*⁹ in 1937 was concerned with the physical therapeutic set-up, the use of optimistic reassurance as psychotherapy and directed play and occupational therapy, but did little in analyzing the psychodynamics of the phenomena they observed in their patients. They did emphasize the need of these individuals for such a mental hygiene program. More recent studies published by 2 social workers working separately (Grant,⁸ Copellman⁴) underline the "severe emotional component in facing a diagnosis of poliomyelitis" and the high incidence of behavior disorders—38% in 100 children. Lowman¹² recently described the well-rounded therapeutic program of the Orthopedic Hospital of Los Angeles in which the mental hygiene department plays a large rôle in assessing the social, educational and vocational aspects of each poliomyelitis patient. He indicates that these individuals very commonly have trouble in adjusting to their future from a personality standpoint as well as from the standpoint of their physical disability. Of pertinent interest is an interesting psychiatric study of amputees in the army by Randall *et al.*¹⁴ He demonstrated that these physically disabled soldiers showed

a high incidence of anxiety and that 64% had trouble in adjusting themselves to their total life situation as cripples.

In response to the obvious need for a study of the emotional impact of this illness on poliomyelitis victims, a study (Hoekstra¹⁰) was undertaken at the University of Colorado in the latter part of the recent Colorado epidemic. The project outlined was essentially a factual one and not a therapeutic set-up due to limited personnel. Its broad aim was to study the emotional impact of the illness. Case material was not selected except that we desired patients with some degree of paresis and a minimum age limit of 14. The latter requirement was chosen because we wished to have a fairly stabilized personality structure, subject to previous stresses and strains of adjustment, on which to observe the effect of the illness. No other limits were imposed. Of a large number of hospitalized poliomyelitis patients, 16 were studied intensively during the acute and early recovery stages of their illnesses.

The method of study is outlined as follows: The patients were apprised of the interviewer's status and their coöperation in a study of poliomyelitis asked. None rejected the study although 1 of the 16, a nurse, became somewhat paranoid as her hospitalization progressed, was very critical of nursing and medical care, felt she was regarded as "psychopathic" and was being used as a "guinea pig." All others established good rapport and seemed to appreciate the special attention given and the superficial reassurance implicit in having an interested individual see them frequently. A "standard" history was taken with psychiatric emphasis on personality structure, past history, and the individual's emotional reaction to past illnesses and to the present illness. A thorough physical and neurologic survey was recorded. A Rorschach test was done as soon as conveniently possible after the onset of the illness. Thematic apperception tests are to be done during the follow-up. A social history from near relatives with emphasis on the pre-polio per-

sonality, past history, social adjustment and reaction to previous illnesses was requested on each patient. Inasmuch as this is a central nervous system disease, an electro-encephalogram on each patient was obtained. After this spade work, the patients were seen daily and their progress and behavior observed. A follow-up is proposed during the convalescent period after discharge from the hospital. At that time their progress, neurologic status, attitude and affect will be observed and another Rorschach test will be done. Some difficulty in carrying out this program in the acute phase of the illness was encountered due to the patient's rigid schedule of physiotherapy (Kenny hot packs) throughout the day as well as routine nursing and medical care.

when assayed against these initial data in revealing psychosomatic relationships and indicating trends of value. However, this pilot factual survey does show the emotional impact of the disease and is of sufficient interest, although incomplete, to report here in some detail.

Almost all the patients studied expressed on query a conscious feeling of shock and fear for their lives when they first learned their illness was poliomyelitis. Most of these 16 patients reacted initially with varying degrees of affective depression and tearfulness or a desire to cry. Almost every one felt that most patients with poliomyelitis die or are so severely crippled that they are complete invalids for the rest of their lives. It is interesting to point out that this is not an intellectual

FIG. 1.—ILLUSTRATIVE CONSOLIDATED CLINICAL RECORD

NAME AND DATE: J. N. Onset, 7/31/46; admitted, 8/5/46; interview, 8/9/46. *Age:* 39. *Sex:* male. **NEUROLOGIC:** *Paresis:* paralysis of right forearm +++ and right arm +++; weakness in right hand ++ and left thigh +. *Spinal Fluid:* 8/2/46, Cells, 26. *Prot.:* 56. **MENTAL STATUS:** *Attitude:* very coöperative; appears somewhat worried about his condition—concerned about return to work. *Affect:* appropriate; smiles readily to jokes. *Other:* —. **RORSCHACH:** 9/13/46; R-32; very ambitious extrovert beyond ability; above average intelligence; passive trends; lively affect with considerable drive but not unstable; compulsive tendency shown in experience balance—a tendency to passiveness for which ambitious drive may be a compensation. **SOCIAL AND P. P. HISTORY:** *Personality:* extrovert; shows a labile effect, responding to environment readily; outgoing in interests; describes himself as an idealist. *Neurotic Trails:* somewhat unhappy childhood due to parental differences, no manifested neurotic traits; average school grades; married twice; first wife left due to irregular work record, reacted to separation with despondency and inclination to drink for about 1 year. *Reaction to Previous Illnesses:* no serious illness until age 22—severe quinsy; was taken to hospital late because mother was Christian Scientist; had to have emergency operation; was despondent and worried if he ever would come out of the hospital. *Other:* father inclined to drink—was a railroad man for many years; was somewhat strict; mother died when patient was 24; was a Christian Scientist; very worrisome; troubled a lot by sick headache. **PRESENT ILLNESS:** About 7/31 complaining with sore neck, tiredness and that light bothered his eyes; had been in bed for about 10 days previously with "flu;" seen by railroad doctor and sent to St. Joseph's Hospital 8/2; on 8/3 noticed tingling in his arms, chills and fever; an L.P. done at that time; when awakened 8/4, right arm was paralyzed; transferred here 8/5. *Habitus:* athletic type, always in excellent health. *Reaction type summary:* somewhat emotionally unstable extrovert who reacts to adverse circumstances with depression; otherwise personality is rather stable; has made a good adjustment in work and present marriage; has reacted to polio with moderate affective depression which responds fairly well to simple reassurance.

In Figure 1 is shown the type of consolidated record made on each patient from the rather voluminous clinical record and various laboratory procedures. As can be seen from this consolidated form, there are a number of variables in each patient, any of which can be used as a point of departure for analysis. We believe that the follow-up during the convalescent period will be most valuable

belief necessarily, but more an emotional state. This is exemplified in the patient in this group who was a practicing registered nurse at the time of contracting the illness (R. E., Seventh patient in Table 1.) She had had much experience in the treatment and nursing care of poliomyelitis and, although intellectually aware that most polio victims do not die and that few are significantly incapacitated by

TABLE 1.—ANALYSES OF DATA

Patient	Age	Social and personal history		Mental status	Salient features of Korschach	Spinal fluid			E.E.G.	Reaction to polymyeltitis
		Pi	Neurotic traits			C	P	Abnor.		
D. R.	16	B P	Epilepsy from age 2	Querulous, noisy; very restless	Confused, marked aggression, sex concern	L* A† B	4† 430	S2	Refused	Marked sexual preoccupation and restlessness, indifference to polo
G. G.	14	B P	Very dependent in minor illness	Negativistic; dependent	Low intellect; marked dependency	L*	95	N	Refused	Developed very strong dependency and chronic insecurity and tension
C. D.	16	I	Very dependent; emotional	Fearful, pain intolerant	Explosive affect; introspection	L*	37	Normal	Refused	Chronic insecurity and tension mobilized by polo; severe emotional lability manifested
B. R.	14	I	Always healthy	Good ward adjustment	Marked passivity, moderate shock	A† B	22	Normal	Refused	Rigidly repressed moderate anxiety and feelings of insecurity
W. B.	37	I	Mod. somatic; preoccupation	Marked somatic; concern, fearful	Depression, neurotic shock	L† B	420	N	Refused	Marked somatic concern and anxiety with moderate mood disturbance
C. W.	31	I	Chr. backache from minor injury	Mild effective; depression	Inhibited, passive; low intellect	Mild B	41	Border-line	Refused	Subjective early concern with relief as polo symptoms rapidly cleared
R. E.	28	I	Unknown	Very tense, hyper-erectile, depressed	Neurotic, tense, emotionally inhibited	L‡	90	Normal	Refused	Marked concern projected on hospital with reaction of R ^x tension and rejection of anxiety
N. E.	15	I	Always healthy	Good ward adjustment	Low intellect; diffuse anxiety	A† L† A† A†	90	Normal	Refused	Mild insecurity feelings and mood depression
B. B.	17	I	Well tolerated	Mild depression	Controlled neurotic shock, mild depression	A† A† A†	40	Normal	Refused	Mild depression and tension evident
R. R.	21	I	Well tolerated	Depressed, good ward adjustment	Intelligent, some depression, mild neurosis	A*	27	Not obtained	Refused	Marked affective reaction with apathic moodiness
S. J.	17	E	Well tolerated	Very depressed, anxious	Severe depression and anxiety	A*	63	L.V.†	Refused	Definite affective depression of moderately severe degree
J. N.	34	E	Poorly tolerated	Labile effect, with depression	Unstable effect; passiveness	B† A†	26	Abnor.	Refused	Accepted polo with mild mood depression and strong desire for misarrange of pregnancy
M. I.	19	E	Always healthy	Mild periods of mood depression	Instability, tension; neurotic shock	L†	98	S2	Refused	Mild to moderate mood depression and insecurity feelings
P. L.	28	E	Marital discord; mild asthmatic	Tearful and moody	Severely constricted; introspective	L†	415	L V†	Refused	Mild to moderate mood depression and moderate tension and insecurity feelings
H. A.	20	E	Very well tolerated	Depressed and tense	Neurotic, depressed; insecure	L*	324	Normal	Refused	Tension, mild depression and manifested somatic concern
O. R.	30	E	Always healthy	Depressed and tense	Rich, well controlled and with autonomic concern	L† A‡	55	Normal	Refused	Manifested somatic concern of spinal fluid.

Pi, personality; B, P, childhood behavior problem; I, introvert; E, extrovert; C, cells; P, protein in mg per 100 cc of spinal fluid.
 * Sex are involvement of both arms or legs; A, arm; L, leg, B, bulbar symptoms.
 † Done 2 weeks after onset.
 ‡ Severe involvement of 1 extremity.
 § Moderate involvement of both arms or both legs.

residual paralysis, was very emotionally upset, tense, tearful and aggressively resentful about her illness in a paranoid manner. Her only physical evidence of poliomyelitis was a mild paralysis of muscles in 1 thigh.

We realize that this is too small a group of patients from which to draw valid conclusions. With this in mind, we have tried to view our findings objectively for trends and not conclusions. In a comparison of the 5 patients with bulbar paralysis (Table 1), 3 with severe spinal involvement as well as the bulbar localization had severe personality disruptions. The patient, B. R., with bulbar symptoms and moderate involvement of his arms showed an apparent good adjustment on the ward during the acute phase but demonstrated rigidly suppressed anxiety and insecurity in the psychologic test. These feelings later became apparent in his behavior during convalescence on the ward. One patient (C. W.) had very mild bulbar signs which disappeared rapidly so that he was able to leave the hospital symptom-free 16 days after the onset of his illness. It is obvious that bulbar symptoms, particularly when the ability to breathe is involved, are a very frightening threat to life. It is not surprising that anxiety and insecurity was seen in large percentage in these individuals. No patient who required the aid of a respirator was included in this survey.

There seems to be little evidence of any relationship between the severity of spinal paralysis and the severity of any psychiatric symptoms. However, in looking at the record from the standpoint of the clinical psychiatric picture, 7 of these 16 patients, almost 44%, showed moderately severe to severe disturbances in thinking and feeling. Two (G. G. and D. R.) were definitely mentally deficient before poliomyelitis. Of the remaining 5, 2 (S. J. and R. E.) had good previous personality adjustment as near as could be determined from direct interview and a social service

history. The remainder of this group of 7 (J. N., W. B. and C. D.) had moderate to moderately severe psychiatric disturbances previously in their lives.

From the Rorschach studies done on these patients, it was possible to interpret their basic personality pattern, to estimate their intellectual ability and their emotional status at the time of the test, *i. e.*, presence of anxiety, neurotic behavior patterns and degree of maturity and mood. Objectivity of interpretation of the records was maintained by having all of the tests examined by a trained psychologist* who had no other knowledge of the patients. All of the records showed distinct features of disturbance, usually in mood, feelings of insecurity and anxiety or somatic preoccupation. Even those with apparent excellent adjustments to their illness (B. R., N. E. and B. B.) showed distinct abnormality in their Rorschach records. In 1 patient, S. J., who reacted to her severe poliomyelitis with marked depression, we obtained 2 Rorschach examinations 5 weeks apart. A comparison of these records is extremely interesting because they show a profound disturbance in her first record and a considerable amelioration in the second. In the first record taken during the early part of her illness, we saw evidence of a traumatic background and some neurotic tendencies verified by her social and personal history and, in addition, a severe reaction to her present situation with the expression of tremendous insecurity, color and shading shock, depression of affect, a severe constriction of emotional feeling and a withdrawal from reality. In a record obtained 5 weeks later there was much improvement. She showed liberation of fantasy material, rejection of only 1 card, reduction in reaction time, increase in the number of responses and the appearance of tension material which had been completely blocked by her regression in the first record. We believe that the convales-

* Appreciation is gratefully acknowledged to Samuel S. Dubin, Clinical Psychologist at the Colorado Psychopathic Hospital, Denver, Colorado.

cent follow-up studies on the other patients will be similarly revealing.

The initial electro-encephalogram studies on these 16 patients are of questionable significance. All were normal except 4. One (C. W.) was a borderline record of doubtful significance, a reëxamination at the time was not obtained because of the patient's early release from the hospital. One (D. R.) grossly abnormal record was obtained in an individual who had suffered from epilepsy since the age of 2. Two records (J. N. and M. I.) were grossly abnormal. Such cortical dysrhythmia is an occasional finding even in normal individuals. It is interesting that neither of these 2 patients had bulbar or encephalitic symptoms.

In spinal fluid studies in this group of patients, little or no direct relationship was noted between the cell count and/or protein content and the severity or extent of central nervous system involvement. It was felt that there was a tendency for a higher protein elevation in those with bulbar signs than those with only spinal involvement. This was certainly nothing more than a trend, however.

It was found, as others have reported, that individuals stricken by this disease usually were enjoying good or robust health when suddenly afflicted. In this group, all of the patients but 1 were in robust physical health. This exception was C. D., a dependent, ailing, emotional child of 16. One patient suffered from idiopathic epilepsy but physically was in good health.

Summary. From this preliminary study of 16 poliomyelitis patients selected at random for a factual psychosomatic study, it can be stated that: 1. These individuals, when they first realized the nature of their

illness, reacted uniformly with depression and anxiety.

2. Those with bulbar signs in addition to the spinal type of paresis tend to have a greater psychologic disturbance than those individuals with only spinal involvement.

3. These psychiatric disturbances developing in relationship to poliomyelitis are reversible to some degree by psychiatric therapy as measured by the Rorschach test.

4. Electro-encephalographic tracings in individuals with spinal and bulbar types of poliomyelitis show no significant dysrhythmia.

5. Spinal fluid findings are not typical as to the various types or degree of involvement in poliomyelitis although the protein content tends to be higher in those individuals with bulbar symptomatology.

Conclusions. 1. A definite need for the study of the psychosomatic aspects of poliomyelitis has been expressed by many workers in this field. Psychiatric disturbances are rather commonly observed.

2. No factual study with a follow-up through the convalescent period has been carried out. Some attempts at a mental hygiene program and psychiatric and social service help in the period of rehabilitation have been carried out with evident success.

3. A preliminary report of a factual study of poliomyelitis in 16 patients is presented. It points out that these patients uniformly experience a severe psychologic impact when learning of the nature of their illness which commonly results in functional or emotional symptoms. That psychiatric therapy is needed during the acute as well as the remote convalescent and rehabilitation phases is obvious.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF NOVEMBER 19, 1946

The Production of Hydropic Degeneration of the Islands of Langerhans by Intraperitoneal Glucose Injections in the Cat. F. C. DOHAN, M.D., and F. D. W. LUKENS, M.D. (George S. Cox Med. Res. Inst., Hosp. of the Univ. of Penna.). Previous studies have suggested that an elevated level of blood glucose may, under certain circumstances, result in lesions of the pancreatic islets. To study this question further cats were given repeated intraperitoneal injections of 20% glucose in physiologic saline. With this high carbohydrate intake, extravitamins particularly thiamine were administered. Many cats died after a few days with a syndrome of anorexia, ataxia, weakness of hind legs and occasional convulsions. However, some cats did not develop this syndrome or recovered from it so that the injections could be continued for weeks. Daily determinations of the blood glucose concentration established the degree and duration of hyperglycemia. Sections of the pancreas from 13 cats have been examined. Seven animals injected from 14 to 104 days had hyperglycemia for 9 or more days and showed marked hydropic degeneration of the beta cells. The other 6 animals were injected for 6 to 24 days but showed hyperglycemia on only 6 days or less. In this group the islands were normal. In addition, in 1 normal cat hyperglycemia was maintained for a period of 39 days by means of glucose injections. After stopping the injections the cat remained severely diabetic and developed diabetic acidosis 22 days after the last injection of glucose. During this period of permanent post-injection diabetes it excreted 100% of the calculated available carbohydrate of its diet.

It is believed that these findings of

hydropic degeneration of the beta cells and permanent diabetes mellitus following prolonged intraperitoneal injections of glucose add further support to the hypothesis that a sustained elevation of blood glucose may, under certain conditions, lead to the production of damage to the islands of Langerhans in this species. Other disturbances which might be responsible wholly or in part for the island lesions are under study.

The Effect of Detergents and Semi-detergents Upon the Resting Potential of Muscle. RUDOLF HÖBER, M.D. (Dept. of Physiology, Univ. of Penna.). The effect of detergents is due to the non-polar configuration of their ions, the non-polar part of the effective ion being organophilic, the polar hydrophilic. In the ordinary technical products, the organophilic part contains alkyl chains of various length and the hydrophilic part sulfonate or sulfate. The alkyl chains by their surface activity adhere to many organic substances, among them cell surfaces, and, due to the pull of the hydrophilic sulfonates towards the water, they can disintegrate non-living and living colloidal aggregates (*irreversible* denaturation, *irreversible* bacteriolysis). By applying detergents containing alkyl chains shorter than present in the technical products (1 to 5 alkyl groups instead of 8 to 12), *reversible* physiologic effects are released, for instance in muscle resting potentials of various strength and direction and rise or fall of excitability.

These properties are shown to be significant not only to detergents having the typical molecular configuration, but also to substances somewhat deviating from the ordinary structure by variations in the

organophilic or in the hydrophilic components. I have called them *semidetergents*. They have been found among the metabolites of the body (for example as detoxication products) and among some kinds of drugs (for example, as derivatives of sulfa drugs). They might be significant as being *activators of resting cells*, to throw them into function.

The Oxygen Metabolism of the Dog's Heart. J. E. ECKENHOFF, M.D., J. H. HAFKENSCHIEL, M.D., and C. M. LANDMESSER, M.D. (Dept. of Pharmacology and Harrison Dept. of Surgical Research, Univ. of Penna., and Dept. of Anesthesiology, Hosp. of Univ. of Penna.). In spontaneously breathing dogs lightly anesthetized with nembutal, coronary blood flow was measured by a method already described (AM. J. MED. SCI., 212, 123, 1946); cardiac oxygen consumption was estimated from this and the coronary arteriovenous oxygen difference. The venous samples were collected directly from the great cardiac vein; from the curves representing the uptake of nitrous oxide during inhalation of that gas, and from the fact that the venous outflow ceased entirely during occlusion of the corresponding coronary artery, we concluded that this was uncontaminated coronary venous blood whereas samples collected from the coronary sinus were not.

The average oxygen consumption of the heart (left ventricle) under "normal" conditions was 9.1 cc. per 100 gm. per minute (s.d. ± 1.1).

Cardiac oxygen consumption showed excellent correlations with coronary blood flow ($r = 0.85$), coronary resistance ($r = 0.77$), and blood pressure ($r = 0.67$). It was not closely related to cardiac output, or to cardiac work (*i. e.*, cardiac output \times mean blood pressure); the data bearing on this suggested systematic variations in cardiac efficiency (*i. e.*, work per unit of oxygen consumed) depending on whether the work changes was produced by change in the peripheral resistance or in cardiac output.

This was borne out by 4 experiments in which peripheral resistance was primarily increased and decreased by clamping and unclamping the aorta just below the diaphragm, and another 4 in which cardiac output was primarily increased by intravenous infusions of gelatin or blood. In the former cardiac output and cardiac work decreased, while in the latter they increased; cardiac oxygen consumption increased in all cases but cardiac efficiency decreased in the former, increased in the latter. Under these circumstances therefore cardiac efficiency varied directly with the cardiac output and inversely with the peripheral resistance.

Under "normal" conditions the oxygen content of arterial, mixed venous and coronary venous blood averaged about 20, 15 and 5 vols. % respectively; even when the circulation was markedly depressed the latter seldom fell below 2 vols. % and sometimes its oxygen content was higher than that of mixed venous blood. Evidence was obtained that the heart has 2 protective mechanisms in circulatory depression: (1) the fraction of cardiac output passing through the coronaries then increases, while (2) cardiac work decreases, and with it the need of the heart for oxygen.

The intrinsic control of the coronary circulation was found to resemble that of the cerebral both in independence of vasomotor innervation and in dependence on the metabolic requirements of the tissue. Under the existing experimental conditions, at least, the resistance in the coronary circulation was governed predominantly by the existing oxygen consumption of the heart.

Cytochrome c in Regenerating Rat Liver and Its Relation to Other Pigments. MARYLIZABETH W. CRANDALL and DAVID L. DRABKIN (from the Dept. of Physiological Chemistry, School of Medicine, Univ. of Penna.). Partial hepatectomy (liver lobectomy) is proposed as a technique in the investigation of the metabolism of tissue constituents. Owing to the multi-

lobed character of rat liver and the anatomic constancy of relationship of individual lobe weights to total liver mass, this technique has the advantages of ease of applicability and quantitative reproducibility. Analytical values upon the tissue excised at hepatectomy serve as "internal" controls, yielding the concentration and total quantity of constituents in the remaining liver tissue (*A values*). Regeneration (restoration) of tissue after excision of approximately two-thirds of the liver is relatively rapid (about 80% restoration in 2 weeks). The concentration and total quantity of the desired constituents are now obtained upon the restored liver after sacrifice of the animal (*B values*). *B values* — *A values* = *new material which appears during regeneration*.

This type of "depletion technique" has been applied to a study of the rate of production of cytochrome *c*. In a postoperative period of 14 days, the total increase in new cytochrome *c* in liver was 571 gamma, or a daily increment of 41 gamma. Since the total cytochrome *c* in the restored liver averaged 1313 gamma, 41 gamma represents a daily increment of 3.5%.

This rate of appearance of new cytochrome *c* compares favorably on a percentile basis with that of hemoglobin production in dogs depleted by Whipple's hemorrhage technique.²

The interpretation of the results has been aided by data on the content of water and protein-bound phosphorus (as an index of cellularity¹) and by supplementary analysis for cytochrome *c* in skeletal muscle, kidney cortex and heart. While it is most likely that the new cytochrome *c* in liver has been produced in the regenerating tissue, the present experiments have not excluded the possibility that the new cytochrome *c* in liver may have been transferred to this tissue from skeletal muscle.

Sufficient analytical data have been accumulated to permit a reliable estimation of the total cytochrome *c*, myoglobin, and hemoglobin of a young, adult albino rat (reference body weight 250 gm.). The quantities in descending order were hemoglobin 3190 mg., myoglobin 101 mg., and cytochrome *c* 14.4 mg. The ratio of these main hemin derivatives is therefore 222:7:1 in this species.

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BOOK REVIEWS AND NOTICES

STARLING'S PRINCIPLES OF HUMAN PHYSIOLOGY. Edited and revised by C. LOVATT EVANS, D.Sc., F.R.C.P., F.R.S., LL.D., Jodrell Professor of Physiology, University College, London. With chapters on the special senses by H. HARTRIDGE, M.A., M.D., Sc.D., F.R.S., Professor of Physiology, St. Bartholomew's Medical College. 9th ed. Pp. 1155; 668 ills., including 7 in color. Phila.: Lea & Febiger, 1945. Price, \$10.00.

AMONG the half-dozen or so recent comprehensive textbooks of human physiology in English the ninth edition of Starling, like its 8 predecessors, occupies a place not completely shared by any of its rivals. Among its prominent characteristics are breadth of view, clarity of statement, emphasis on normal physiologic processes rather than on clinical problems, and especial fullness of treatment of basic chemical and physical principles. Its position as perhaps the most general of all the modern textbooks is further strengthened in the present edition by an innovation in the form of brief historical reviews at the beginning of each of its main sections. These are said in the Preface to have been introduced as an experiment; to the Reviewer, at least, the success of the experiment already seems obvious. The general arrangement of the subject matter is much the same as in the earlier editions, but a considerable amount of new material has been added. An unusually large number of well-chosen illustrations and numerous references to the original literature in convenient footnote form are additional valuable features of a generally admirable work.

M. J.

PHYSICAL TREATMENT BY MOVEMENT, MANIPULATION AND MASSAGE. By JAMES B. MENNELL, M.A., M.D., B.C. (CANTAB.), Consulting Physical Therapist, St. Thomas's Hospital, and late Lecturer, Massage Training School. 5th ed. Pp. 512; 288 ills. Phila.: Blakiston, 1945. Price, \$7.00.

THE first edition of this book was published during World War I, and this fifth during World War II. Thus, his work has spanned that quarter of a century which

has seen so many changes and advances in Medicine as a whole, and has witnessed the renaissance or resurgence of interest in Physical Treatment.

Successive editions have kept pace with the newer techniques which have been developed during the intervening years. The original sections on Massage were so firmly grounded on scientific and physiologic principles and so clearly presented that there was little need for additions in the present edition. Indeed, it is not too much to say that, throughout the English-speaking world, Mennell's book is generally regarded as the standard work on massage.

The author summarizes well the physical treatment of infantile paralysis, but has not given sufficient credit to Sister Kenny. Whatever deficiencies there are in the Kenny Method, it is used *in toto*, or in a modified form, in nearly all the institutions and organizations in this country where infantile paralysis cases are treated, and also in many parts of the British Empire. To put it differently, Sister Kenny has done more to systematize the physical therapy of infantile paralysis than any other person.

The Preface to the first edition, which is included in the present edition, reveals the author as something of a prophet. In these days of renewed interest in Physical Medicine it is interesting to read what he wrote 28 years ago.

All physicians practicing Physical Medicine, as well as physical therapists, should own this book. They will be amply repaid by reading it because of the solid scientific material it contains, presented in Mennell's facile style, which might well be the envy of many writers of non-technical books.

S. H.

AMERICAN FOUNDATIONS FOR SOCIAL WELFARE. By SHELBY M. HARRISON and F. EMERSON ANDREWS, Russell Sage Foundation. Pp. 249; 4 ills. Brattleboro: Hildreth, 1946. Price, \$2.00.

THE authors, who are associated with the Russell Sage Foundation, have compiled in this book valuable information concerning the origin and organization of Foundations

in America. Chapters are devoted to the description of the types of Foundations, organization and administration, and the fields of activity. The problems related to the financial aspects of Foundations are also discussed. There is included a comprehensive list of 505 American Foundations including a description of their purpose and activities, a statement of their capital assets, and recent expenditures. W. S.

ELECTROCARDIOGRAPHY. Including an Atlas of Electrocardiograms. By LOUIS N. KATZ, A.B., M.A., M.D., F.A.C.P., Director of Cardiovascular Research, Michael Reese Hospital, Chicago; Professorial Lecturer in Physiology, University of Chicago. 2nd ed. Pp. 883; 525 ills. Phila.: Lea & Febiger, 1946. Price, \$12.00.

THIS comprehensive text of electrocardiography has been revised and enlarged. A bibliography has been appended to each chapter. There are numerous summarizing tables. Illustrative tracings usually include the chest leads CF₂, CF₄ and CF₅. There are full discussions of physiology in relation to electrocardiography. The sections on myocardial damage are notable for the reproductions of serial tracings taken at various stages of the illness. W. J.

GENERAL AND PLASTIC SURGERY. By J. EASTMAN SHEEHAN, M.D., Professor of Plastic Reparative Surgery, New York Polyclinic Medical School and Hospital. Pp. 345; 496 ills. New York: Hoeber, 1945. Price, \$6.75.

THIS book admirably covers a broad field. The author draws heavily upon recent war experiences in Spain and England for material to demonstrate traumatic and reconstructive surgery. Such fundamentals as early wound débridement and treatment of abdominal cavity trauma are stressed, as well as the definitive or reconstructive stages of plastic repair of special regions. The patient is considered as a therapeutic entity and is followed from the time of wounding to the stage of final cosmetic repair. Appropriately placed emphasis on the plastic reconstructive phase of injuries accompanies descriptions of early management, and there is no preponderance toward specialized uncorrelated plastic procedures.

The volume will be valuable for the military or industrial surgeon who may have a special interest in plastic surgery. The problems of hand infections, burns, head trauma and peripheral nerve injuries so common in industrial practice are treated in adequate detail for use by one trained in general surgery. The very diversity of the text and its excellent correlation between the principles of general and plastic surgery, in the words of Churchill, provide a guide for the "general plastic surgeon."

The author's civilian experience is well shown in the chapter on plastic surgery of the nose and cleft deformities of the face and palate. The brief, clean-cut descriptions, elimination of outmoded methods of repair, and simplified illustrations make the text readily usable.

The entire volume is profusely illustrated with drawings and photographs. H. R.

FRACTURES OF THE JAWS. By ROBERT H. IVY, M.D., D.D.S., F.A.C.S., Professor of Plastic Surgery, School of Medicine and Graduate School of Medicine, and of Clinical Maxillo-Facial Surgery, School of Dentistry, University of Pennsylvania; Chief of Plastic Surgery, Graduate Hospital, etc.; Medical Officers Reserve Corps, U. S. Army; and LAWRENCE CURTIS, A.B., M.D., D.D.S., F.A.C.S., Associate Professor of Plastic Surgery, Graduate School of Medicine; Assistant Professor of Maxillo-Facial Surgery, School of Dentistry, University of Pennsylvania; Chief of Oral and Plastic Surgery, Bryn Mawr Hospital, etc. 3rd ed. Pp. 174; 199 ills. Philadelphia: Lea & Febiger, 1945. Price, \$4.50.

THE 3rd edition of this "old favorite" is well received at this time. Its reemphasis upon the simpler methods in the management of jaw fractures coincides with the return to civilian life of numerous physicians and dentists who had been engaged in handling gunshot fractures in the armed forces. Many of these individuals, who may have had no prior interest in maxillo-facial injuries may desire to continue their work in this field, and this book provides an excellent background for both dentist and surgeon.

As indicated in the Preface to the 1st edition of this work, most of the measures used in treatment can be performed without

the services of a highly technical dental laboratory, and they are, therefore, within the reach of the professional staff of any hospital or of any dentist. The surgeon in charge of these cases, although he may not be a maxillo-facial specialist, must see to the completion of the detailed treatment if he receives them under his care. The simplicity of approach and clear descriptions and illustrations make this task an easier one.

The additional chapters on radiographic technique by Dr. LeRoy M. Ennis and on dietary management by Dr. Clyde W. Scogin are timely. Often mistakes in treatment occur that are due to ineffective liaison between oral surgeon and radiologist. The latter may fail to understand the type of film desired and the reasons thereof, and the clinician frequently does not make his meaning clear to the radiologic consultant. Study of this chapter by both radiologist and oral surgeon is recommended.

The outline of feeding by Dr. Scogin completes the picture of modern management in jaw fractures. Although the diets given are qualitatively adequate, it is questioned whether they contain sufficient protein for optimum wound healing, and it is anticipated that they will need to be supplemented with powdered milk or a protein digest.

H. R.

CORNELL CONFERENCES ON THERAPY. Volume I. Edited by HARRY GOLD, Managing Editor, DAVID P. BARR, McKEEN CATTELL, EUGENE F. DU BOIS, and CHARLES H. WHEELER, Editorial Board, Cornell University Medical College. Pp. 322. New York: Macmillan, 1946. Price, \$3.25.

This volume is simply an edited record of a selected series of round table forums on various problems of therapy, ranging in time from 1939 to 1946. It includes discussions by several different physicians, pharmacologists and students on each of the following subjects: (1) The Doctor's Bag, (2) Use and Abuse of Bed Rest, (3) Hypnotics and Sedatives, (4) Psychologic Aspects of the Treatment of Pain, (5) Surgical Measures for the Relief of Pain, (6 and 7) Treatment of Heart Failure (I and II), (8) Digitalis vs. Digitoxin, (9) The Use of the Mercurial Diuretics, (10) Treatment of Subacute

Bacterial Endocarditis, (11) Management of Abdominal Distention, (12) Treatment of Some Intestinal Infestations, (13) Treatment of Some Common Diseases of the Eye, (14) Treatment of Poisoning, and (15) The Rh Factor in Therapy.

Each chapter is printed in conference form with an authority on the topic delivering a prepared introduction. The remainder of each conference is devoted to informal and extemporaneous discussion covering pathologic physiology, drugs and therapeutic procedures as related to the particular subject. Consequently one gets several different authoritative views on controversial matters. These discussions are, for the most part, interesting and stimulating. The editors have not attempted to provide a textbook on therapy.

H. H.

NEW BOOKS

Daniel Coit Gilman. By ABRAHAM FLEXNER, M.D. Pp. 173; 3 ill. New York: Harcourt, Brace, 1946. Price, \$2.00.

THIS small book about a great educator and the first president of Johns Hopkins University, written by another famous Hopkins man, is a timely contribution to thought upon higher education.

The Centennial of Surgical Anesthesia. Compiled by JOHN F. FULTON, M.D., and MADELINE E. STANTON, A.B. Pp. 102; 9 ill. New York: Schuman, 1946. Price, \$4.00.

AN annotated catalogue of books and pamphlets bearing on the early history of surgical anesthesia that is compact and thorough.

Clinica y Laboratorio. Interpretación y crítica de los métodos y resultados de los Analisis Clinicos. Por el DR. GUSTAVO PITTALUGA, Catedrático de la Facultad de Medicina de la Universidad de Madrid, con la colaboración de los DOCTORES ENRIQUE GALAN, ANTONIO GUERNICA. Pp. 459; 94 ill. Habana, Cuba: M. V. Fresneda, 1946. Price, \$9.00.

THIS is a useful book for readers of Spanish. The work of the distinguished Professor of Medicine at the University of Madrid, its 22 chapters cover various methods of examinations of body fluids and functional tests of viscera; also virus, fungus and parasitic infections, hormone, biopsies and so on.

NEW EDITIONS

Hygiene. By J. R. CURRIE, M.A. (OXON.), M.D., LL.D. (GLAS.), D.P.H. (BIRM.), F.R.C.P. (EDIN.), Professor-Emeritus of Public Health, University of Glasgow, and A. G. MEARNS, B.Sc., M.D., D.P.H. (GLAS.), F.R.S. (EDIN.). 2nd ed. Pp. 432; 89 ills. Baltimore: Williams & Wilkins, 1945. Price, \$6.00.

THIS edition has been valuably enlarged to include the information upon the subject that has been developed due to experiences of World War II.

Medical Uses of Soap. Edited by MORRIS FISHBEIN, M.D. Pp. 195; 41 ills. Philadelphia: Lippincott, 1946. Price, \$3.00.

THIS second printing of a well-integrated Symposium includes a new chapter on the Surgical Uses of Soap. The book appears to gratify a need.

Manual of Applied Nutrition. Compiled by HELEN BAUGHMAN, KATHLEEN M. LEWIS and ELOISE R. TREASCHER. Pp. 103. Baltimore: The Johns Hopkins Hospital, Dietary Dept. 2nd ed. 1946. Price, \$1.50.

Essentials of Medicine. By CHARLES PHILIPS EMERSON, Jr., A.B., M.D., Assistant Professor of Medicine, Boston Univ. School of Med., and JAMES ELIZABETH TAYLOR, R.N., B.S., M.Ed., Nursing Education Consultant, U. S. Public Health Service. Pp. 688; 201 ills. Philadelphia: Lippincott, 1946. Price, \$3.50.

THE fact that this is a 15th edition establishes the book's usefulness by the empirical method.

Nutritional Charts. By the STAFF, Research Dept. Pp. 47. Pittsburgh: Heinz. 12th ed., 1946. No price given.

Hygiene. By F. L. MEREDITH, B.Sc., M.D., Professor of Hygiene and Public Health, Tufts College. Pp. 838; 155 ills. Philadelphia: Blakiston, 1946. Price, \$4.00.

A welcome 4th edition of a valuable and sound book for college students and, indeed, all educated persons interested in their own health as well as in public health.

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

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ORIGINAL ARTICLES

A STUDY OF AN OUTBREAK OF INFLUENZA B IN ROCHESTER, NEW YORK

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INFLUENZA B virus was first isolated independently by Magill⁹ and Francis² in 1940, and since then it has been recognized as the cause of outbreaks of influenza both in the United States and abroad. As Horsfall⁶ pointed out, influenza is an exactly defined symptom-complex. It is now accepted that the exact diagnosis of influenza is most satisfactorily established by the demonstration of at least a 4-fold rise in antibody titer as determined by the Hirst test,⁵ or by isolation and identification of the causative virus. Epidemic influenza may be caused by various strains of either influenza A or B virus, but in some outbreaks neither virus has been incriminated in as many as 30% of the cases.⁷ Furthermore, it has been reported that both A and B viruses may occur simultaneously in the same population, or, rarely, in the same individual.^{7,10,13} Gordon³ has shown that there are quantitative differences as well as antigenic relationships between strains of influenza B virus. That a strain of influenza B virus may be associated with fatal bacterial infection has been reported by Himmelweit⁴ who isolated the virus from a patient who quickly succumbed to pneumonia. Postmortem examination showed destruc-

tion of the epithelium of the tracheobronchial tree, pulmonary hemorrhage and necrosis, as well as paucity of cellular reaction. The lungs contained enormous numbers of staphylococci. Nigg, Ekland, Wilson and Crowley¹⁰ reported a 50% mortality in 8 patients (average age over 45 years) who developed pneumonia in the course of influenza B.

Because of the prospect of an epidemic of influenza in this community, it was planned to study a group of patients should an outbreak occur. The purposes of the investigation were not only to attempt to determine the causative agents, but also to appraise clinically the value of sulfonamide prophylaxis in diminishing the frequency of bacterial complications. Hence a plan to treat alternate cases with sulfadiazine was projected.

The present report is based upon the findings in 46 patients who were admitted to the Strong Memorial and Rochester Municipal Hospitals from Dec. 10 to 18, 1945, inclusive. Actually about 80 patients with a similar pattern of disease were observed during the months of November and December, but we have limited the number of cases considered here for the following reasons. First,

lacking positive etiologic evidence, there is no certain way of differentiating influenza B from many other acute respiratory illnesses. Secondly, before December 10, most of the patients suspected of having influenza seemed to represent sporadic cases from the community at large. Thirdly, a sudden influx of cases between December 10 and 18, inclusive, was largely from a somewhat isolated group of young men living on the River Campus of the University of Rochester. These patients represented only the more severely ill cases from that campus. Fourthly, the admission rate dropped abruptly after December 18, and from then on only apparently sporadic cases were seen. Hence, a precipitous onset in a detached and fairly homogeneous group characterizes the bulk of the cases reported. Of the 46 patients, 37 were male, and 9 were female. Their ages ranged from 17 to 62 years; five-sixths of the group were 18 to 22 years of age. Thirty-four were students at the River Campus, 10 were personnel of the hospitals, and the remaining 2 were from the community at large. The student body and the hospital personnel were vaccinated against influenza A and B between December 15 and 19; 8 of the patients were members of these vaccinated groups. The latter had symptoms of from 1 to 3 days duration that were thought, in most cases, to be

due to actual infection rather than to have resulted from the vaccine.

The clinical study of the patient included, in addition to the routine history and physical examination, white blood cell counts and differential counts, bacterial cultures of the blood and nasopharynx, serologic tests for cold hemagglutinins and heterophil antibodies. From 4 patients the nasopharyngeal washings were inoculated in embryonated hen's eggs and intranasally in mice in an attempt to isolate a virus. From these same 4 patients and 5 additional ones, serum was obtained on admission, and again 3 or 4 weeks later, for the performance of the Hirst test. Twenty-three patients had chest roentgenograms. Because of the rapidity of admissions and the shortage of personnel, all of the projected studies were not performed in every case.

SYMPTOMS AND SIGNS. Twelve patients had symptoms for a day before admission to the hospital, 18 for 2 days, 10 for 3 days, and 8 for 4 to 7 days. Three-fourths of the group had only low grade fever (not over 38° C.). Ten patients had temperatures of 39° C. or higher, with relative bradycardia and normal respiratory rates. The clinical symptoms and signs in the 46 patients under consideration are grouped together in Table 1 in order of decreasing frequency. Except for 1 individual who had had a cough and

TABLE 1.—INCIDENCE OF SYMPTOMS AND SIGNS IN 46 CASES OF INFLUENZA B

Dry cough	37	Injected nasal mucosa	30
Headache	32	Suffusion of eyes	13
Chilliness	29	Flushed faeies	10
Fever	27	Cervical lymphadenopathy	7
Sore throat	27	Generalized lymphadenopathy	5
Coryza	23	Perspiring freely	3
Myalgia	18	Injected tympani	3
Malaise	14	Pulmonary râles	4
Anorexia	12	Pulmonary rhonchi	3
Substernal pain	12	Palpable submaxillary glands	2
Ocular myalgia	11	Prostration	2
Asthenia	8	Sinus tenderness	1
Vomiting	6	Palpable spleen	1
Photophobia	4	Papular rash	1
Hoarseness	3	Nuchal rigidity	1
Otalgia	2	Lethargy	1
Diarrhea	2	Delirium	1
Abdominal cramps	2	Lacrimation	1
Injected pharynx	37		

slight loss of weight for a month, all were in good health prior to the onset of symptoms. A typical case is described:

CASE 1. V. V. (216850), a 19 year old student from the River Campus, was admitted on Dec. 12, 1945, with the complaints of sore throat, non-productive coughing, generalized aching, malaise, coryza, retrobulbar pain, retrosternal pain on coughing and fever of 2 days duration. His temperature was 40.6° C., pulse 110 and respirations 20. He appeared acutely ill. The facies were flushed and the conjunctivæ suffused. The pharynx was injected, and there was catarrhal otitis media bilaterally. Râles were audible in the region of the right upper lobe. On admission, the white blood cell count was 3600 of which 73% were neutrophils, 24% lymphocytes and 2% monocytes. Roentgenogram of the chest showed an increase of the bronchovascular markings. Blood culture was negative, while alpha-hemolytic colonies, *Staph. aureus* and a non-hemolytic streptococcus appeared in the nasopharyngeal culture. Whereas the sheep cell titer was 1:16, and the cold hemagglutination test negative, the Hirst test showed that during convalescence he developed a sig-

cell counts tended to be low. Differential counts revealed from 60 to 90% neutrophils; as a general rule, however, there was no significant shift in the differential formula. *Strep. pyogenes* was found in the throat cultures of 4 patients; other bacteria isolated by aerobic culture of nasopharyngeal swabs on blood agar plates are listed in Table 3. Blood cultures were done on 31 patients. From 3 of these, bacteria of possible significance were isolated, in 2 instances *Strep. viridans* and in the third, a non-hemolytic streptococcus. From only 1 of the 3 cases was there available blood serum taken both early in the disease and during convalescence. The serums from this patient were tested for agglutinins against the organism isolated from the culture of his blood (*Strep. viridans*) according to a technique used by Finland.¹ Serum taken at the onset of influenza agglutinated the strain to a titer of 1:160, while serum taken 3 weeks later showed an identical titer of agglutinins. It is, therefore, impossible to assess any significance to the finding of a

TABLE 2.—ADMISSION WHITE BLOOD CELL COUNTS

Range	No. patients	Range	No. patients
2000 to 4900	19	8000 or more	3
5000 to 7900	21	Not done	3

TABLE 3.—NASOPHARYNGEAL FLORA

Bacteria	No. patients	Bacteria	No. patients
<i>Staph. albus</i>	13	<i>H. influenzae</i>	4
<i>H. parainfluenzae</i>	11	<i>Staph. albus hemolyticus</i> . .	3
<i>Strep. viridans</i>	11	<i>N. catarrhalis</i>	3
"Diphtheroids"	9	<i>Staph. aureus hemolyticus</i> . .	3
Non-hemolytic streptococci	8	<i>M. tetragenus</i>	1
<i>Staph. aureus</i>	6	Not done	18
<i>Strep. pyogenes</i>	4		

nificant rise in titer of antibodies against influenza B virus. He was treated with 37 gm. of sulfadiazine over a period of 7 days, although he exhibited fever for only 3 days. The white blood cell count increased to 6200 during the period of administration of sulfadiazine. Following discharge on the 8th day, he experienced asthenia for 2 days, but felt well thereafter.

LABORATORY FINDINGS. As may be seen in Table 2, the admission white blood

streptococcus in this patient's blood. Furthermore, the failure to demonstrate an increase in antibodies against it during convalescence would make one look askance upon the other 2 instances in which the streptococci were obtained by blood culture.

Tests for cold hemagglutinins were done during the 1st week in 19 patients. The test was negative in 11, and insignificant titers were found in 8, the highest being

1:20. However, when checked about 1 month later, the latter's serum had a titer of 1:160. This patient's hospital course of 6 days was unremarkable, but 2 weeks later he had fever, cough, and headache and remained in bed for a week. This person may have had influenza, but clinical relapse and rising cold hemagglutinin titer during convalescence suggested the possibility of primary atypical pneumonia. Serums obtained, after an interval of 3 or 4 weeks, from 7 additional patients, whose initial level of cold hemagglutinins had been determined, did not reveal any rise in titer.

Heterophile antibody tests were done in 17 instances. The results were negative in 3, insignificant in 13, and positive to 1:256 dilution in 1 patient.

CASE 2. A student from the River Campus had chilliness, fever, headache, backache, malaise, sore throat, coryza and dry cough for 2 days prior to admission. The temperature was 38.5° C., pulse 108 and respirations 21. He, too, appeared toxic and had injection of the nasopharynx. The white blood cell count was 4700 with 74% neutrophils, 18% lymphocytes and 6% monocytes. The chest Roentgen ray revealed increased bronchovascular markings in the right lower lobe. *Strep. viridans* was obtained on culture of the blood. The Hirst test was negative. He was treated with 22 gm. of sulfadiazine over

a 6 day period during which the leukopenia became more marked. When the sheep cell titer was repeated 1 month later, it was 1:128. He had been well in the interval.

Another student with a negative Hirst test and an equivocal titer of agglutinins for sheep erythrocytes (1:32) had a total white blood cell count of 4000 per mm.; 48% of the cells were lymphocytes. His course was uneventful, and he did not report for interview several weeks later. He may, however, have had infectious mononucleosis rather than influenza. Mention should be made of the fact that sporadic cases of infectious mononucleosis had been observed in the student body during the few weeks preceding the outbreak of influenza. Two patients were thought to have had only systemic reactions to vaccinations for influenza A and B, rather than influenza.

All the remaining patients were considered to have had influenza B. As is shown in Table 4, Hirst tests (4) were performed on 9 of these selected at random. During convalescence none developed an increase in circulating antibodies against influenza A virus. Two were entirely negative, 1 of these was from the individual known to have had infectious mononucleosis, the other from the student described above who was suspected of having

TABLE 4.—RESULTS OF HIRST TESTS DONE WITH ACUTE PHASE AND CONVALESCENT SERUMS OF 9 PATIENTS SELECTED AT RANDOM

Patients	Influenza A				Influenza B	
	PR S		WS		Lee	
	a	c	a	c	a	c
M.	32	32	32	32	16	16
S.	64	64	32	64	32	32
V. V.	64	64	64	32	8	32
W.	16	16	16	16	8	32
B.	16	32	16	16	8	64
D.	32	16	32	16	32	128
H.	8	8	32	32	32	128
T.	32	32	128	128	32	128
F.	16	16	16	16	8	32
Controls:						
Ferret-PR S*		512		128		8
Ferret-Lee*		8		32		256
Normal ferret*		0		64		0

a, Acute phase serum; c, convalescent serum.

* Serums furnished by Dr. Thomas Francis, Ann Arbor, Mich.

Positive tests are those with 4-fold or greater rise of titer.

infectious mononucleosis. Altogether 7 patients exhibited significant rises in circulating antibodies against influenza B virus. Inasmuch as none of these serums had been obtained from patients who were vaccinated against influenza A and B, the etiology of the outbreak of influenza-like symptoms, in the majority of the patients, appeared to be influenza B virus. Influenza virus was not isolated in the 4 instances attempted.

Of the 23 patients who had chest roentgenograms, 6 were negative, but 17 showed increased bronchovascular markings. One also showed minimal evidence of infiltration in the left upper lobe. All of these were negative when repeated either before discharge from the hospital, or 3 weeks later.

RESULTS OF PROPHYLACTIC TREATMENT WITH SULFADIAZINE. Twenty patients were treated symptomatically. As a group they exhibited fever for an average period of 1.5 days, and were hospitalized for an average of 4.1 days. One of the 20 had meningismus, and another sinusitis. The latter also had questionable signs of early bronchopneumonia, and was given 400,000 units of penicillin over a 3 day period.

In accordance with the plan to treat alternate cases prophylactically with sulfadiazine, in order to determine its value in diminishing the incidence and severity of complications of influenza, those patients selected were given on admission 4 gm. of the drug by mouth. This was followed by 1 gm. every 4 hours until the temperature had been normal for at least 2 or 3 days. In addition, when a complication appeared, some of the previously untreated controls were then started on the same dose of sulfadiazine, except for the 1 individual treated with penicillin as mentioned above. Altogether, 26 patients received from 10 to 36 gm. of the drug. Of these, 22 were treated prophylactically, 2 because of otitis media, and 1 each because of bronchitis or laryngitis. This group of patients manifested fever for 2.2 days, and was hospitalized for an

average of 6.6 days. The longer hospital stay was due, in part, to the policy of continuing sulfadiazine therapy until 2 or 3 days of normal temperature had been observed. Six patients developed microscopic hematuria which necessitated discontinuance of the drug; 2 had traces of albuminuria. The renal complications could be attributed in every instance to unanticipated confinement of the patient in a hot room of low humidity. The effect of the sulfonamide therapy on the white blood cell count, already depressed by influenza, was not remarkable.

Thirty-one patients from the River Campus were interviewed 4 or 5 weeks after discharge in order to evaluate further the effectiveness of sulfadiazine prophylaxis. Almost all of these young men had traveled widely during the Christmas holiday, many on crowded trains. Of the 31, none had developed pneumonia; 16 denied any residual symptoms or complications; they felt well after discharge from the hospital. Seven of those treated with sulfadiazine had temporary asthenia, as against 2 of the control group. Persistent coughing was noted by 4 in the untreated group, and by only 2 of those who were treated with sulfadiazine.

There was 1 other patient, however, from the hospital personnel, who had prophylactic sulfadiazine for 3 days and was discharged after 10 days. He had to be re-admitted a day later because of acute, purulent otitis media. *Strep. pyogenes* was cultured from the ear. He had a white blood cell count of 1900.

Discussion. Since significant rises in antibody titer against influenza B virus were demonstrated in 7 patients selected at random, we feel that influenza B virus was responsible for the epidemic studied. The syndromes of influenza A and influenza B have been described as indistinguishable in groups as well as in individuals.⁸ Some emphasize the more common occurrence of sweating, giddiness, nausea, vomiting and substernal chest pain in influenza B infection.¹² We do not feel that our data permits this distinction, ex-

cept, perhaps, with respect to substernal pain which occurred in 12 of our patients. The occasional similarity as witnessed in the present study, of the symptom-complexes of those known to have either influenza B, infectious mononucleosis, or primary atypical pneumonia is striking. Inasmuch as neither influenza virus nor immunologic evidence of infection due to it has been found in a substantial number of individuals in some previously reported epidemics of influenza, consideration of other etiologic agents is warranted. In the present investigation, limited largely to young adults, influenza B was largely a self-limiting respiratory illness with few bacterial complications, the most frequent being otitis media. On the basis of the data presented, no benefit can be accorded the use of sulfadiazine in preventing bacterial complications in patients with influenza B infection. The data are, of course, insufficient to permit a final opinion.

Shope has suggested a concept of wide-

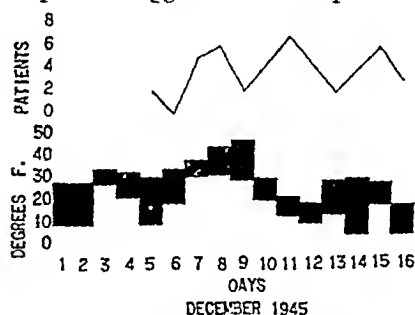


FIG. 1.—Comparison of onset of symptoms with fluctuations in temperature in Rochester. The blocked areas represent range of temperature in ° F. in the Rochester area; the heavy line, the variations in numbers of patients who had onset of symptoms on those days.

spread pre-seeding of the causative agent to account for the rapidity of appearance of new cases of both swine influenza and human influenza in the course of epidemics. The same author has also suggested the possible rôle of meteorologic factors in evoking outbreaks of the disease.¹¹ In Chart 1 we have plotted the frequency of occurrence of our cases, dated at the onset of symptoms, against the daily variations in temperature in Rochester, N. Y., for December 1945. It may be of interest to note that the cases appeared during rather wide fluctuations in temperature over a short period of time.

Summary and Conclusions. During a 9 day period in December 1945, 46 patients (chiefly young men from a college campus) were admitted to the hospital with an acute respiratory illness; 2 were thought to have reactions to influenza A and B vaccination; 2, infectious mononucleosis; 1, atypical pneumonia, and the remaining 41 to have influenza B. In 7 of the 41 selected at random, the Hirst test was positive for influenza B. Increased bronchovascular markings in chest Roentgen rays were seen in many. Seven developed minor complications, the commonest being otitis media. None had significant sequelæ. Twenty-six were treated with sulfadiazine prophylactically, or for complications. Although the total number of cases was too small to permit a final opinion, the incidence of complications, and the subsequent convalescence did not appear to be favorably influenced by sulfadiazine prophylaxis as compared with experience in an untreated control group.

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RELATIVE CLINICAL AND HEMATOLOGIC EFFECTS OF CONCENTRATED LIVER EXTRACT, SYNTHETIC FOLIC ACID AND SYNTHETIC 5-METHYL URACIL IN THE TREATMENT OF MACROCYTIC ANEMIAS IN RELAPSE*

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BECAUSE of the world-wide distribution of the macrocytic anemias, physicians everywhere have contemplated the best method for their detection and therapy. In his excellent book, which was published in 1855, Thomas Addison¹ of London described the clinical picture of one of the macrocytic anemias which he called pernicious anemia. Biermer, in 1872, in a lecture given before the Medical Society of Zurich, described this anemia in greater detail and called it "progressive" pernicious anemia. He pointed out that this condition in some way involved the digestive system.

The idea of taking mammalian liver internally goes back to antiquity in the mythology of many races. In 1926 Minot and Murphy² initiated the cra of its modern usefulness in man when they showed that the oral administration of large doses of whole liver effected a remission of Addisonian pernicious anemia in relapse. Liver was soon tested in various types of macrocytic anemia and was found to be an effective hematopoietic substance in the treatment of the macrocytic anemia of pregnancy, of tropical sprue, of non-tropical sprue, of nutritional deficiency, and of pernicious anemia.

It soon became apparent, however, that a potent extract from liver would be less difficult to administer than whole liver. A number of crude liver extracts were prepared, and within 2 years Colin had developed his Fraction G.³ This Frae-

tion G became widely used in treating macrocytic anemias due to the absence or deficiency of erythrocyte maturation factor (EMF). EMF was considered to be the end-product of a reaction between the extrinsic factor, which was found in food, and the intrinsic factor, which was found in the secretions of the gastric mucosa. On the basis of this concept, which was fostered by Castle, it was possible to classify further the macrocytic anemias on the basis of intrinsic factor or extrinsic factor deficiency. Thus, Castle considers that the macrocytic anemia of pernicious anemia is characterized by a deficiency of intrinsic factor, while the macrocytic anemias of pregnancy, nutritional deficiency, and sprue are characterized by a deficiency of extrinsic factor. The intrinsic and extrinsic factor studies will not be discussed in this paper. With this concept in mind, many investigators directed their efforts toward the intrinsic factor, the extrinsic factor, or the EMF. Many fractions obtained from liver were hematologically active, but the great majority of them had no hematopoietic activity whatever. Many other substances such as brewers' yeast, hog stomach, kidney and brain were tried with success. Several of these substances had been known for many years to have hematopoietic properties, but none of them came up to the hematopoietic standards of concentrated liver extract. Because of the efficacy of concentrated liver extract in

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inducing remissions in the EMF deficiency anemias, it became the standard of those students who were constantly assaying new substances and new liver fractions. It soon was apparent that the various preparations themselves varied considerably, depending on the source of extraction, the method involved, and many other uncontrollable factors. It became obvious to some that liver might contain many substances that might be hemato-poietically active. This concept was strengthened by the observations that some substance or substances were destroyed in the concentration of crude liver extract as determined by the hemato-poietic response effected by both crude and concentrated liver extract.

Jacobson and SubbaRow⁴ consider that there is no single intrinsic or extrinsic factor but that there are many factors that are necessary to produce a full, maximal hematologic response when the substances in question are given in minimal doses. In the fall of 1945, the authors and many other investigators were working on the problem. Realizing that liver extract was a mixture of many chemical substances, we knew that we were facing a difficult and tedious task. Throughout the years we had been studying fractions of reticulogen prepared by Dr. J. K. Cline, and we had tested the hemopoietic properties of many nutrients and synthetic substances. Some of these had slight activity, but most of them had none. We were also working with concentrates; 1 of these was folic acid concentrate which was furnished to us by Dr. E. A. Sharp. We had long known that a number of concentrated liver extracts which were of high potency in treating pernicious anemia contained only infinitesimal amounts of folic acid. Nevertheless, our working hypothesis was that a number of chemical molecules could probably effect hemopoiesis and that folic acid might well be one of these even if it were not the active one in concentrated liver extract. When folic acid became available in sufficient quantities for clinical testing, its effect on

patients with macrocytic anemia was so dramatic that its efficacy was very quickly demonstrated.^{5,6,7} Thus, for the first time it was possible to administer a pure synthetic compound to persons with the macrocytic anemia of pernicious anemia, of nutritional deficiency, of pregnancy, or tropical sprue, and of non-tropical sprue and to effect a hematologic remission. This discovery was of great importance for many reasons. Probably the most important is that its discovery has at long last placed investigations in the field of the macrocytic anemias in the realm of pure compound therapy. With the advent of pure compound therapy a step closer has been taken toward learning the etiology and pathogenesis of the disease.

The initial observations were difficult to evaluate in terms of past therapeutic performance because even though a pure synthetic compound was available it was necessary to assay it against and compare it to concentrated liver extract about which little is known in respect to the number and nature of the factors it contains. However, it has been conclusively established that folic acid is an effective hemato-poietic substance in the treatment of all of the EMF deficiency anemias.^{8,9,10} To date, there have been no negative reports concerning its use in these anemias. The hematologic response to folic acid is much the same as it is to liver extract. It has no effect on aplastic anemias, hypochromic anemia, primary thrombocytopenia, idiopathic leukopenia and leukemia.^{10,11} Folic acid is also ineffective where liver extract is ineffective.

Once the efficiency of folic acid in the treatment of macrocytic anemia was established, a search was continued for other pure synthetic compounds of known structure. By March 1946,¹² the hemato-poietic properties of 5-methyl uracil (thymine) were reported. This substance is one of the 4 nucleotides occurring in thymonucleic acid and is a basic cell constituent. We have since shown that synthetic 5-methyl uracil in daily oral doses of 15 gm. is effective in causing a remission

sion in the macrocytic anemia of tropical sprue,¹³ pernicious anemia¹⁴ and nutritional macrocytic anemia.¹⁵ Because of significant differences in the hematologic response of such patients to synthetic 5-methyl uracil and synthetic folic acid, it is considered important to report these differences. Since there are also certain minor differences in the response of patients with macrocytic anemia to synthetic folic acid and concentrated liver extract, it is also considered proper to report those differences. The neurologic aspects will not be discussed in this paper. It is fully realized that there are many hematopoietic compounds, but it has been our aim to assay pure compounds against pure compounds; and we believe that concentrated liver extract when compared with these other anti-anemic preparations probably contains the least number of different substances. From a controlled scientific point of view it is not desirable to compare a pure compound such as folic acid or 5-methyl uracil with an impure compound such as liver extract. The comparison is made because liver extract is the most widely used, the best known, and primarily because it is the most effective anti-anemic therapeutic agent we have at our disposal to date.

We are reporting on a total of 100 patients treated with concentrated liver extract, 24 patients treated with synthetic folic acid, and 14 patients treated with synthetic 5-methyl uracil. These patients had either true addisonian pernicious anemia, nutritional macrocytic anemia, or the macrocytic anemia of tropical sprue. Representative cases were chosen for sake of simplicity and detail. This report is concerned with a comparison of the hematopoietic and clinical effect of each of these 3 substances in 1 case of addisonian pernicious anemia in relapse and in 1 case of nutritional macrocytic anemia in relapse, and with the effect of synthetic folic acid in 1 case of sprue and of synthetic 5-methyl uracil in 1 case of sprue.

SELECTION OF PATIENTS. All the patients selected for study met the following

basic criteria: (1) A mean corpuscular volume of 100 μ or more. (2) A mean corpuscular hemoglobin of 32 μ g. or more. (3) A mean corpuscular hemoglobin concentration of 34% or more. (4) A color index of 1 or greater. (5) A red blood count of 2.5 million or less. (6) Megaloblastic arrest of the sternal bone marrow. (7) The patient must be untreated or he must not have been treated recently enough to interfere in any way with the evaluation of anti-anemic therapy.

In the selection of persons with pernicious anemia, an additional criterion was a histamine refractory achlorhydria and achylia which had remained unchanged over a period of 1 to 4 years during which time gastric analyses were done every 6 to 12 months. The selection of patients with nutritional macrocytic anemia was made by the use of the basic criteria, but in addition each patient selected must have free hydrochloric acid, rennin and pepsinogen in the gastric secretions after histamine stimulation as well as evidence of concomitant nutritive failure.

The selection of persons with tropical sprue was determined by the following criteria in addition to the basic criteria mentioned above: (1) There must be free hydrochloric acid and enzymes in the gastric secretions after histamine stimulation. (2) The single dose oral glucose tolerance curve must be flat. (3) The patient must have glossitis and diarrhea characterized by stools which show an increase in total fat and a preponderance of fatty acids as determined by chemical analysis. (4) There must be a weight loss of at least 30 pounds in the 6 months prior to study.

The 4 patients thus selected were hospitalized on each occasion prior to the institution of therapy. Careful medical and dietary histories as well as complete physical and neurologic examinations were done prior to treatment. During hospitalization the diet was rigidly controlled and contained no meat, meat products, fish or fowl and allowed only 1 egg and $\frac{1}{2}$ pint of

milk a day. The egg, as well as the vegetables, were cooked at high temperatures for a long period of time in an effort to destroy any extrinsic factor that might occur in these foods. Those patients who had tropical sprue were denied milk and eggs entirely in addition to the above dietary restrictions. Baseline clinical, hematologic and laboratory studies were performed as described elsewhere.^{5,9} To our knowledge none of these patients had ever had a spontaneous remission. The baseline periods varied because treatment was always withheld until it appeared that the patient was actually getting worse both clinically and hematologically.

When such a point was reached, therapy was instituted. The dosage of liver extract, folic acid and 5-methyl uracil was varied in almost each patient because at the time we were endeavoring to determine minimal and maximal doses. We have since learned that 0.5 cc. of concentrated liver extract (reticulogen),* 10 to 20 mg. of synthetic folic acid (Folvite),† and 15 gm. of synthetic 5-methyl uracil (thymine)‡ are practical for the average case. These amounts are in the average case about the minimal doses which will give a reticulocyte response that is not influenced by an increase, no matter how great, in the substance employed. It has also been determined that folic acid is effective when given parenterally or orally,⁸ and for that reason the parenteral route was abandoned in these studies.

The concentrated liver extract used in these studies was kept at a temperature below 55° C. Immediately prior to administration, the required dose was removed from the chilled vial and the medication was injected into the right or left gluteal muscles. The site of injection was alternately changed each day. Synthetic folic acid and synthetic 5-methyl uracil were weighed on an analytical balance immediately prior to administration. These drugs were partially dissolved and sus-

pended in $\frac{1}{4}$ to $\frac{1}{2}$ glass of water and administered orally.

Case Reports. CASE 1. J. B. (addisonian pernicious anemia). This 46 year old white married male was first seen by us on May 29, 1944, and was hospitalized on that date. At that time he had many complaints, the most prominent of which were dizziness, weakness, shortness of breath, cardiac palpitation, pedal edema, redness and soreness of the tongue, and tingling and numbness of the hands and feet. Physical examination done at that time revealed severe generalized pallor, a divergent strabismus of congenital origin, sears and fissuring of both angles of the mouth which were interpreted as evidence of old cheilosis, severe pyorrhea, severe redness of the tongue and complete atrophy of the lingual papillae,+++ pitting edema of the legs and feet, hypesthesia to light touch and pin prick of a stocking type over the left foot, and diminished vibratory sense over the ankles and knees. Position sense was intact and there was slight calf muscle tenderness to pressure. There was no change in the reflexes, and there were no pathologic reflexes found. Laboratory studies revealed a histamine refractory achlorhydria and achylia and a negative blood Klein as well as negative urinalyses, stool analyses, chest plate, and gastro-intestinal Roentgen ray series. An icterus index was slightly elevated. Hematologic studies showed an erythrocyte count of 1.25 million, hemoglobin of 5.1 gm. (33%), a reticulocyte count of 1.8%, a leukocyte count of 3250, PCV of 16, MCV of 128, MCH of 40.8, and MCHC of 31.8. Sternal bone marrow showed arrest at the megaloblastic level. Table I shows the packed cell volume and blood indices determined on each occasion prior to the initiation of specific therapy.

The patient was treated with some success with 2 liver fractions obtained from reticulogen in this laboratory. He was discharged on June 28, 1944, in a somewhat improved condition.

He was followed in our clinic for almost 6 months and received no liver or other substances containing the so-called anti-anemic principle. By December 6, he had a recurrence of the symptoms enumerated

* Supplied by Eli Lilly & Co.

† Supplied by Lederle Laboratories, Inc.

‡ Supplied by Hoffmann-La Roche, Inc.

above and was hospitalized. Physical examination was essentially as recorded on his first hospitalization. The erythrocyte count was 1.69 million, hemoglobin 5.4 gm., and the leukocyte count 4950. The reticulocytes were 0.2%, and sternal bone marrow was characteristic of megaloblastic arrest. Gastric analysis performed after histamine stimulation showed achlorhydria and achylia. By December 9, the erythrocyte count was 1.39 million, the hemoglobin was 4.4 gm., the reticulocytes were 0.2%, and therapy was instituted. The patient received 1 cc. of reticulogen I.M. every day for a period of 6 days. As seen in Figure 1, a peak reticulocytosis of 37.3% was reached on the 6th day after therapy was initiated. Simultaneously with this reticulocytosis there was a striking upsurge in well-being and improvement in appetite. On Feb. 3, 1945, 57 days after therapy was initiated, the red blood cell count was 5.08 million and the hemoglobin 13.1 gm. It should be noted that this patient received a total of only 6 cc. of a potent liver extract and thereafter received no anti-anemic therapy. Concomitant with the remission in this patient's blood picture there was complete clinical improvement. The redness of his tongue disappeared and it became pale and repapillated. Table 2 shows in summary form the hematologic response to this treatment as well as to the other forms of treatment employed.

When he was discharged from the hospital, he felt and appeared strong and well. He was followed in our clinic for almost 9 months without receiving any specific anti-anemic therapy. Gradually he relapsed hematologically and clinically and was readmitted to the hospital on Sept. 22, 1945, with symptoms of severe glossitis, stomatitis, profound weakness, dyspnea, vertigo, tinnitus, anorexia and moderate to severe paresthesias of the hands and feet. Physical examination revealed essentially the same findings as were noted on the first admission in May of 1944. Laboratory studies showed a histamine refractory achlorhydria and achylia, an essentially normal gastro-intestinal tract as determined by Roentgen ray examination, and normal urinalyses and stool analyses. The erythrocyte count was 1.96 million, the hemoglobin 7.9 gm. (51%), the leukocyte count 4800, and reticulocytes 0.4%. Blood indices were compatible with a morphologic

diagnosis of macrocytic hyperchromic anemia in relapse. Sternal bone marrow studies showed arrest of the marrow cells at the megaloblastic level. On Sept. 23, 1945, the red blood cell count was 1.64 million, the hemoglobin 7.1 gm., and therapy was instituted. The patient received 50 mg. of synthetic folic acid by mouth twice daily for a period of 20 days as shown in Figure 1. On the 5th day of this therapy a peak reticulocytosis of 19.2% was attained. Hemopoiesis was rapid and the patient was discharged on October 12, with a red blood cell count of 4.07 million, a hemoglobin of 9.8 gm. (64%), a leukocyte count of 9850, and a reticulocyte count of 1%. Clinically the patient responded equally as well as he did hematologically. At the end of a 65 day period his erythrocyte count had reached a level of 4.97 million, and his hemoglobin was 12.5 gm. Again it should be realized that this patient was under treatment for a period of only 20 days after which he received no specific anti-anemic therapy.

He was again followed in clinic and received no specific therapy for 3 months, and by the end of this time he had relapsed once more and had many of the symptoms he had at the time of each previous relapse. He was admitted to the hospital on March 14, 1946. Physical examination showed essentially the same abnormalities as were present on the 3 previous hospitalizations except that on this occasion there was hyperesthesia to pin prick of a glove type over both hands and wrists. Laboratory data revealed a histamine refractory achlorhydria and achylia, an icterus index of 13.4 units (normal 8 to 10 units), an essentially normal gastro-intestinal series, normal chest Roentgen ray, normal oral glucose tolerance test, and essentially normal urinalyses and stool analyses. Sternal bone marrow was again characteristic of megaloblastic arrest, and on the day of admission to the hospital the hematologic studies revealed a red cell count of 1.55 million, a hemoglobin of 6.2 gm. (40%), a white cell count of 3050, a reticulocyte count of 0.3%, PCV of 20, MCV of 129, MCH of 40, and MCHC of 31. By March 17, the baseline studies were completed, and therapy was instituted. The patient received 2 gm. of synthetic 5-methyl uracil 3 times a day orally for a period of 19 days. A peak reticulocytosis of 16% was reached on the 11th day

of this treatment; 21 days after therapy had been instituted the erythrocytes had shown an increase of 530,000 cells per c.mm. of peripheral blood, while the hemoglobin showed an increase of 3.1 gm. per 100 cc. of peripheral blood. Figure 1 shows well that the hematologic response in this man to 5-methyl uracil at this dose level was far below that obtained with folic acid or concentrated liver extract. It should be recalled, however, that the dose employed was not standard. The clinical response was also less dramatic. The patient's tongue remained essentially unchanged; and his appetite which had originally improved, became worse during subsequent treatment. Paresthesias of his hands remained unchanged. After treatment was discontinued, the erythrocytes failed to continue to mature and relapse was rapid. Figure 1 shows that the maximum erythrocyte count attained was 2.39 million 21 days after therapy was instituted. The slow rate of increase is illustrated in the flat type of curve also shown in this figure.

Sternal bone marrow obtained on the day following the peak reticulocytosis was done during each course of therapy. The marrow was normoblastic and in a reactive state at this stage of treatment. It was impossible to differentiate these marrow preparations on the basis of the therapeutic substances employed. To all intents and purposes the bone marrow response was essentially identical to each form of therapy.

CASE 2. E. S. (nutritional macrocytic anemia). This 75 year old white married male was seen by us for the first time on June 28, 1943, the date of hospitalization, with complaints of weakness, anorexia, cardiac palpitation, dyspnea, vertigo, soreness and redness of the mouth and the tongue, severe paresthesias and numbness of the hands and feet, burning of the soles of the feet, and soreness of the calf and thigh muscles bilaterally. He had a chronic intermittent diarrhea consisting of 3 to 6 loosely formed, brown-colored stools a day which were never characterized or described as being frothy, foamy, voluminous or foul-smelling. All of these symptoms were approximately of 1 year's duration during which time he had lost 15 to 20 pounds of weight. A diet history revealed a deficient intake of thiamine (B_1) and niacin. He had eaten no meat for the preceding 8 years and had eaten only small amounts of cooked liver

occasionally during this period of time. Physical examinations revealed a severely pale man whose skin had a slightly yellow tinge. There were 2 large purpuric lesions over the left forearm and hand. His tongue was pale and edematous with many fissures over the dorsum, and there was evidence of old cheilosis bilaterally. Peripheral arteriosclerosis was present to a moderate degree. The neurologic examination revealed hyperesthesia to pin prick in the regions around both elbows. A stocking type hypesthesia to light touch was present over the lower extremities, and there was a reduction in vibratory sense of 30% in the arms and 80 to 90% in the legs bilaterally. Calf muscle and nerve trunk tenderness was exquisite. Position sense was intact. There were no pathologic reflexes present. The knee jerks and ankle jerks were hyperactive bilaterally; otherwise the reflexes were physiologic. Laboratory data revealed a negative blood Klein, an essentially normal gastro-intestinal Roentgen ray series and chest Roentgen ray, and normal urinalyses and stool analyses. A gastric analysis showed hypochlorhydria and the presence of rennin and pepsinogen after histamine stimulation. The icterus index was 16 units. The sternal bone marrow revealed arrest at the megaloblastic level. Hematologic studies showed an erythrocyte count of 670,000, a hemoglobin of 2.9 gm. (18%), and a leukocyte count of 1750. The patient remained in the hospital until March 11, 1944, during which time many substances were assayed for hematologic activity. The hematologic responses obtained with these substances are not within the scope of this report and consequently are deleted from Figure 2. Suffice it to say that the patient was discharged with a red blood count of 3.4 million and hemoglobin of 11.3 gm. on that date.

He was followed in clinic under non-specific therapy and gradually relapsed. He was readmitted to the hospital on Oct. 1, 1944, with the symptoms and signs as were described on his first admission. A diet history revealed an inadequate intake of thiamine (B_1) and niacin and a borderline adequacy of protein and vitamins A, B_2 (G) and C. Laboratory studies showed a slightly elevated icterus index and the presence of free hydrochloric acid and enzymes in the gastric secretions after histamine stimulation. Blood studies on October 1 revealed a red blood

Date
5/29/41
12/6/44
9/22/45
3/14/46

TABLE 1.—PACKED CELL VOLUME AND BLOOD INDICES OF CASE 1

ICV	MCV	MCH	MCHC	Color index
16	128 0	40 8	31 8	1 32
17	100 5	31 9	31 7	1 60
23	117 3	40 3	34 3	1 80
20	129 0	40 0	31 0	1 29

Type of treatment
Liver fractions from reticulogen
Reticulogen
Synthetic folic acid
Synthetic 5-methyl uracil

TABLE 2.—HEMATOLOGIC RESPONSE OF CASE 1 (ADDISONIAN PERNICIOUS ANEMIA) TO CONCENTRATED LIVER EXTRACT, SYNTHETIC FOLIC ACID, AND SYNTHETIC 5-METHYL URACIL

Date of initiation of therapy	Erythrocytes (millions)			Hemoglobin (gm.)			Reticulocytes			No. days administered
	Initial (on 1st day of therapy)	10 days	Maximum (days)	Initial (on 1st day of therapy)	10 days	Maximum (days)	Initial % (on 1st day of therapy)	First rise	Day of peak	
12/9/44	1 39	2 94	5 08 (57)	4 4	7 0	13 1 (57)	0 2	4	6	6
9/23/45	1 61	2 51	4 97 (65)	7 1	9 0	12 5 (65)	0 2	4	5	20
3/17/46	1 86	2 09	2 39 (21)	5 8	6 8	8 9 (21)	0 6	4	11	19

Treatment and dose
Reticulogen, 1 cc. I.M. q.d.
Synthetic folic acid, 50 mg. b.i.d. orally
Synthetic 5-methyl uracil, 2 gm. t.i.d. orally

Date
6/28/43
10/1/44
2/4/46
6/4/46

TABLE 3.—PACKED CELL VOLUME AND BLOOD INDICES OF CASE 2

PCV	MCV	MCH	MCHC	Color index
10	141 0	43 0	29 0	1 30
14	125 0	37 5	30 0	1 20
22	115 8	37 9	32 7	1 20
26	104 0	30 5	29 2	0 96

Type of treatment
Various liver fractions from reticulogen
and other preparations
Reticulogen
Folic acid
5-methyl uracil

count of 1.12 million, a hemoglobin of 4.2 gm. (27%), a white blood count of 3250, a reticulocyte count of 2.6%, and a PCV of 14. Blood indices were as follows: MCV 125, MCH 37.5, MCHC 30. The color index was 1.2. The packed cell volume and blood indices determined prior to therapy on each occasion are shown in Table 3. Sternal bone marrow obtained during baseline studies showed arrest at the megaloblastic level. By October 4, the red blood cell count was 1.03 million and the hemoglobin 4.2 gm., and therapy was instituted. The patient received 1 cc. of reticulogen I.M. every day for 15 days. The reticulocyte response was evident on the 3rd day of therapy, and a peak reticulocytosis of 21.4% was reached on the 8th day of treatment as shown in Figure 2 and Table 4. When the reticulocytes began to increase, the patient volunteered that he felt much better in many ways. His appetite improved; he regained his strength; the symptoms referable to his glossitis and peripheral neuritis began to disappear. On November 30, 58 days after therapy was instituted, the erythrocyte count was 5.95 million and the hemoglobin was 12.7 gm. The patient felt well and strong and had only residual numbness of his extremities which was believed to be caused by arteriosclerosis.

During 1945 the patient had 2 relapses and was treated with both whole blood and concentrated liver extract, as well as with several other substances. The treatment of these relapses and subsequent responses have been deleted from Figure 2 for the sake of clarity and conciseness. The patient received no specific anti-anemic therapy after September 1945, and by November 28 his red cell count had reached a level of 4.17 million and the hemoglobin was 11.5 gm.

Thereafter he relapsed once more and was readmitted to the hospital on Feb. 4, 1946. He had a recurrence of all the symptoms described above. A diet history revealed a dietary very low in meat products and deficient in protein, iron and niacin, and of borderline adequacy in thiamine (B₁). The physical examination was essentially as determined on his first admission in 1943. Hematologic studies done on the day of admission showed a red blood count of 1.79 million, a hemoglobin of 6.9 gm. (44%), a white blood count of 4550, and a reticulocyte count of 0.1%. The packed cell vol-

ume and the blood indices are shown in Table 3. Gastric analysis done on this admission showed a histamine refractory achlorhydria and achylia. This was repeated after an interval of 2 days, and again a histamine refractory achlorhydria and achylia was obtained. Sternal bone marrow aspirated during the baseline studies was characteristic of megaloblastic arrest. An oral glucose tolerance test showed a slight lag period in absorption, but otherwise it was essentially normal. Urinalyses and stool analyses were essentially normal, and an icterus index obtained prior to therapy was 12.4 units. After satisfactory baseline studies were made, therapy was instituted. On that date, February 13, the red blood cell count was 1.46 million, the hemoglobin 4.3 gm., and the reticulocyte count 0.4%. The patient received 5 mg. of synthetic folic acid twice daily by mouth for a period of 12 days. The reticulocytes began to rise on the 5th day of this treatment, and a peak reticulocytosis of 60.4% was reached on the 8th day as is shown in Table 4. The patient's clinical response did not parallel the tremendous reticulocyte response. He did, however, experience the usual increase in well-being and increase in appetite along with the reticulocytosis. His glossitis improved steadily but at a slightly slow rate. His peripheral neuritis remained essentially unchanged. On the 41st day after treatment had been instituted the red blood count was 3.81 million and the hemoglobin was 11.2 gm. (71%). This was the highest erythrocyte level reached after this course of therapy.

The patient was again followed in the clinic and received no specific anti-anemic therapy. By June 4, 1946, he had relapsed and was admitted to the hospital on that day with an erythrocyte count of 2.49 million, a hemoglobin of 7.6 gm. (48%), a white blood count of 7000, and a reticulocyte count of 0.4%. Sternal bone marrow obtained at that time showed megaloblastic arrest. A gastric analysis done after histamine stimulation showed the presence of free hydrochloric acid as well as rennin and pepsinogen in the gastric secretion. The oral glucose tolerance tests were again essentially normal. The icterus index was 14.1 units, and the urinalyses and stool analyses were essentially normal. By June 17, the red blood cell count was 1.60

million, hemoglobin 5.8 gm. and reticulocyte count 1.2%, and therapy was instituted. The patient received 7.5 gm. of synthetic 5-methyl uracil twice daily by mouth for a period of 9 days. A peak reticulocytosis of 31.2% was reached on the 7th day of therapy. The hematopoietic response of this patient is shown in Table 4 and in Figure 2. There was an improvement of

appetite which lasted for a short period of time as well as an increase in well-being following the initiation of therapy. The symptoms of his glossitis and peripheral neuritis remained essentially unchanged. The highest red blood count attained was 3.13 million on the 21st day after the initiation of treatment. The hemoglobin at that time was 9.2 gm. By the 54th day after

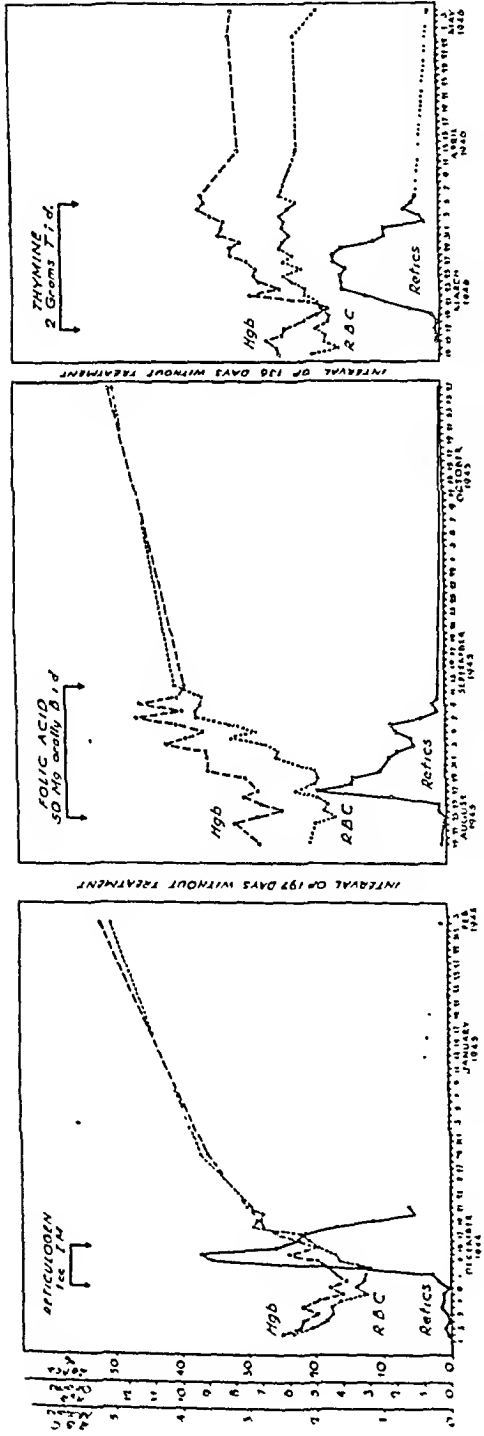


FIG. 1.—J. B., white male, age 46. Histamine refractory achlorhydria and achylia.

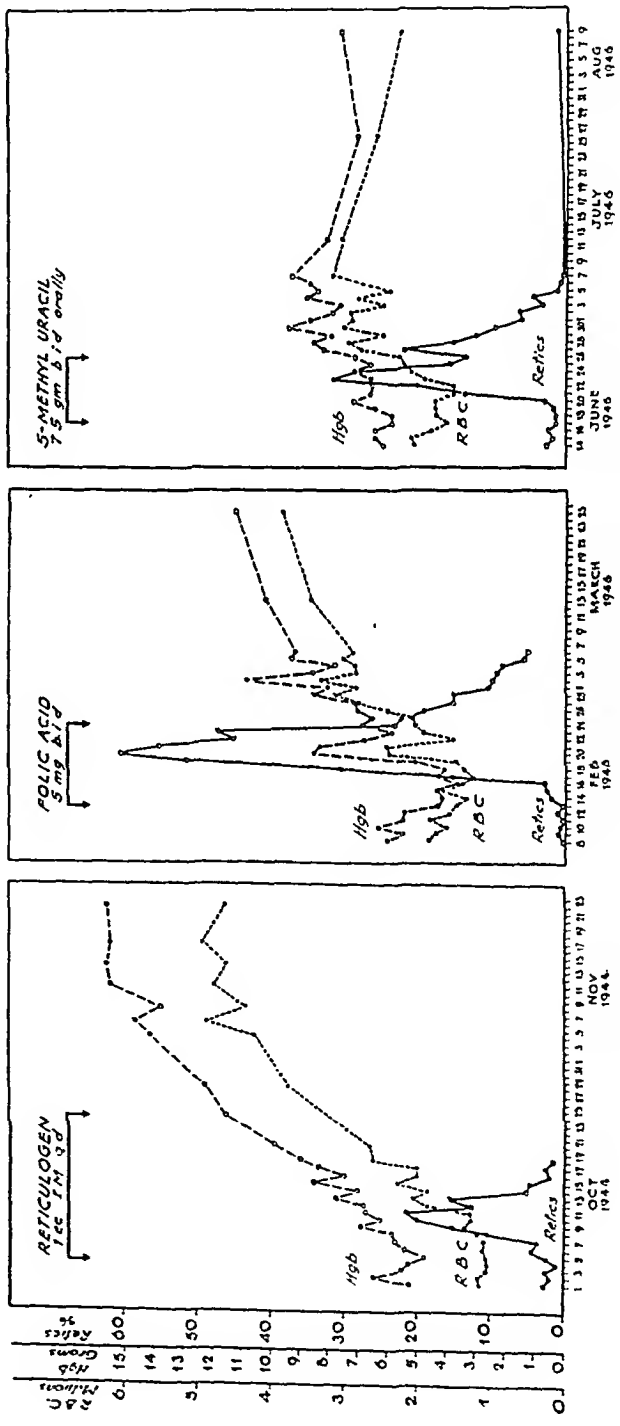


FIG. 2.—E. S., white male. Free hydrochloric acid after histamine.

therapy had been instituted, the erythrocyte count had fallen to 2.22 million and the hemoglobin to 7.5 gm. The patient had clinically and hematologically relapsed once more.

CASE 3. J. C. L. (tropical sprue). This 63 year old white male was admitted to the Calixto Garcia Hospital in Havana, Cuba, on Nov. 18, 1945, with complaints of weakness, vertigo and diarrhea. He dated the onset of his illness to 7 months prior to hospitalization. At that time he noticed burning and soreness of the tongue and the occurrence of small, tender ulcers in his mouth. At about the same time, he began to have from 10 to 12 bulky, frothy, foul-smelling, light-colored stools a day. Defecation was accompanied by colicky pain in the abdomen and by rectal burning. The patient lost his appetite, became weak, had shortness of breath, and lost 30 pounds in weight during the 7 months he was ill. His diet was evaluated as being deficient in animal protein, thiamine (B_1) and niacin. Physical examination revealed an emaciated, pallid male. His tongue was slick and red, and he had a fine, generalized, sealy desquamation of the skin over the entire body. Laboratory studies showed a flat oral glucose tolerance curve, free hydrochloric acid and enzymes in the gastric juice after histamine stimulation, and a normal urinalysis. The stools had a pH of 5.5 and were "fatty." Blood studies on admission showed a red blood cell count of 1.38 million and a hemo-

globin of 6.4 gm. Baseline studies were completed by November 29, and on that date the erythrocyte count was 1.57, the hemoglobin 7 gm. (45%), and the reticulocyte count was 1.1%. The PCV was 21, and the blood indices were as follows: MCV 134, MCH 44.5 and MCHC 30. These blood indices as well as those of Case 4 are shown in Table 5. Therapy was instituted on that date, 10 mg. of synthetic folic acid being given daily by mouth for 82 days. Figure 3 and Table 6 show the hematologic response effected in this patient. A peak reticulocytosis of 27.2% was reached on the 8th day of therapy. Sternal bone marrow study at this time was normoblastic and in a reactive state. Within 10 days after treatment had been instituted, his stools became normal in color. They were copious and semisolid on some days and small and well formed on others. His appetite improved; his strength returned; he gained weight; and there was a striking improvement in his glossitis. On the 61st day after treatment was initiated, his red blood cell count was 3.96 million and his hemoglobin was 12.7 gm. By this time his stools had become almost normal. Eighty-nine days after therapy was started, the erythrocyte count was 4.88 million and the hemoglobin 13.3 gm. These were the highest levels obtained in this patient and represented a net increase in erythrocytes of 3.31 million and in hemoglobin of 6.3 gm. in a period of 89 days.

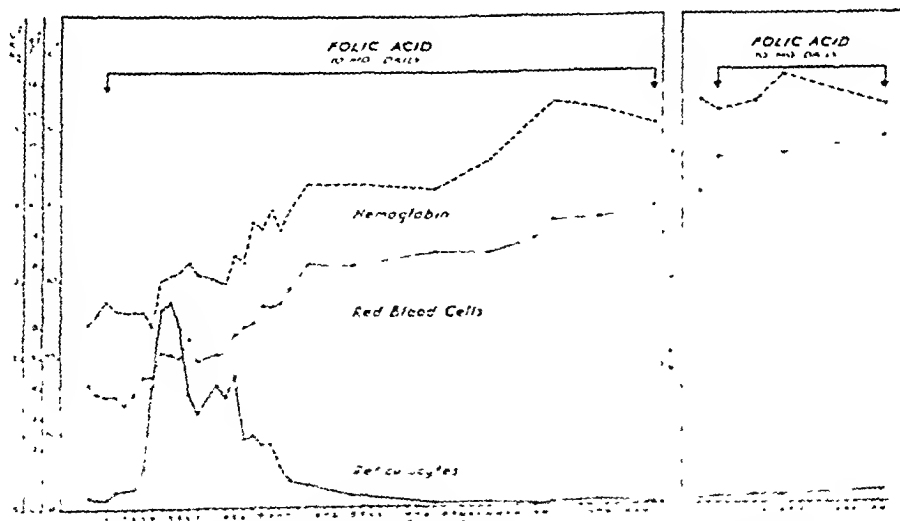


FIG. 3.—The effect of folic acid on the macrocytic anemia of tropical sprue.

TABLE 4.—HEMATOLOGIC RESPONSE OF CASE 2 (NUTRITIONAL MACROCYTIC ANEMIA) TO CONCENTRATED LIVER EXTRACT, SYNTHETIC FOLIC ACID AND SYNTHETIC 5-METHYL URACIL

Date of initiation of therapy	Erythrocytes (millions)			Hemoglobin (gm.)			Reticulocytes				No. days administered
	Initial (on 1st day of therapy)	10 days	Maximum (day)	Initial (on 1st day of therapy)	10 days	Maximum (day)	Initial % (on 1st day of therapy)	First day of rise	Day of peak	% at peak	
10/4/44	1 03	2 05	5 95 (58)	4 2	6 2	12 7	1 0	3	8	21.4	15
2/13/46	1 46	1 80	3 81 (41)	4 3	6 8	11 2	0.4	5	8	60.4	12
6/17/46	1 60	2 23	3.13 (21)	5 8	7 1	9 2	1 2	5	7	31.2	9

TABLE 5.—PACKED CELL VOLUME AND BLOOD INDICES OF CASE 3 AND CASE 4

Date	Case No.	PCV	MCV	MCH	MCHC	Color index
11/29/45	3	21	143	44.5	30	1.4
4/8/46	4	30	142	47.0	33	1.5

TABLE 6.—HEMATOLOGIC RESPONSES OF CASES 3 AND 4 (TROPICAL SPRUE) TO SYNTHETIC FOLIC ACID AND SYNTHETIC 5-METHYL URACIL

Date of initiation of therapy	Reticulocytes (millions)		Hemoglobin (gm.)		Reticulocytes				Treatment and dose	No. days administered
	Initial (on 1st day of therapy)	Maximum (day)	Initial (on 1st day of therapy)	Maximum (day)	Initial % (on 1st day of rise)	Day of peak	% at peak			
11/20/43	1 57	2 23 4 88 (89)	7 0	8 1 13.3 (89)	CASE 3 1.1	5	8	27.2	Synthetic folic acid, 10 mg. daily by mouth	82
1/12/46	1 97	2 58 4.03 (63)	8 7	11 3 13.7 (63)	CASE 4 1.2	5	9	17.0	Synthetic 5-methyl uracil, 15 gm. daily for 14 days; 5 gm. daily for 125 days	139

CASE 4. A. H. (tropical sprue). This 37 year old white male was admitted to the Calixto Garcia Hospital in Havana on March 23, 1946, complaining of diarrhea and anorexia of 3 years duration. His illness began with severe meteorism followed by diarrhea consisting of 4 to 6 liquid or semiliquid, yellowish, foul-smelling stools a day. Defecation was accompanied by a sensation of rectal burning. Anorexia became severe; his mouth and tongue became sore; he developed paresthesias of the hands and legs, pain in the epigastrium, and profound weakness, all of which waxed and waned during that period of time. Four months prior to admission to the hospital, during a relapse, he received liver extract and some unknown medication for a period of $1\frac{1}{2}$ months from his private physician, and striking improvement followed this therapy. However, $2\frac{1}{2}$ months prior to admission he began losing weight, and within this period of time he lost 25 pounds. He relapsed rapidly 1 month prior to admission. The dietary history indicated that for many years his diet had been inadequate in all nutrients. Physical examination revealed a severely emaciated, pale man who appeared extremely depressed. Sealing of the skin was generalized. Over the arms, knees and shoulders there were areas of hyperpigmentation of the skin. The tongue was slick and edematous and was a brilliant red at the tip and edges.

There were several blotchy red areas over the dorsum. The buccal mucous membrane also was red, but there were no ulcerations. Abdominal examination revealed a tympanitic percussion note but no other abnormalities. Neurologic examination was essentially negative. Laboratory studies revealed a flat oral glucose tolerance curve, the presence of free hydrochloric acid and enzymes in the gastric secretion after histamine stimulation, and a normal urinalysis. Stool examination showed a pH of 7.5 and an increase in total fat with a relative increase in fatty acids. Blood studies done on April 8, 1946, revealed a red cell count of 2.11 million, hemoglobin of 10 gm. (65%), a reticulocyte count of 1.2%, and a leukocyte count of 7700. The packed cell volume was 30, MCV 141, MCH 47, MCHC 33 and color index 1.5 as shown in Table 5. Sternal bone marrow showed typical megaloblastic arrest. By April 12 the red blood cell count was 1.97 million, the hemoglobin 8.7 gm., the reticulocyte count 1.2% and therapy was started. The patient was given 7.5 gm. of 5-methyl uracil by mouth twice daily for 14 days and then 5 gm. a day for 49 days. The initial reticulocyte rise occurred on the 5th day of therapy and reached a peak of 17% on the 9th day. The hematologic response is shown in Figure 4 and Table 6. Aspirated sternal bone marrow obtained on the day following the peak reticulocytosis

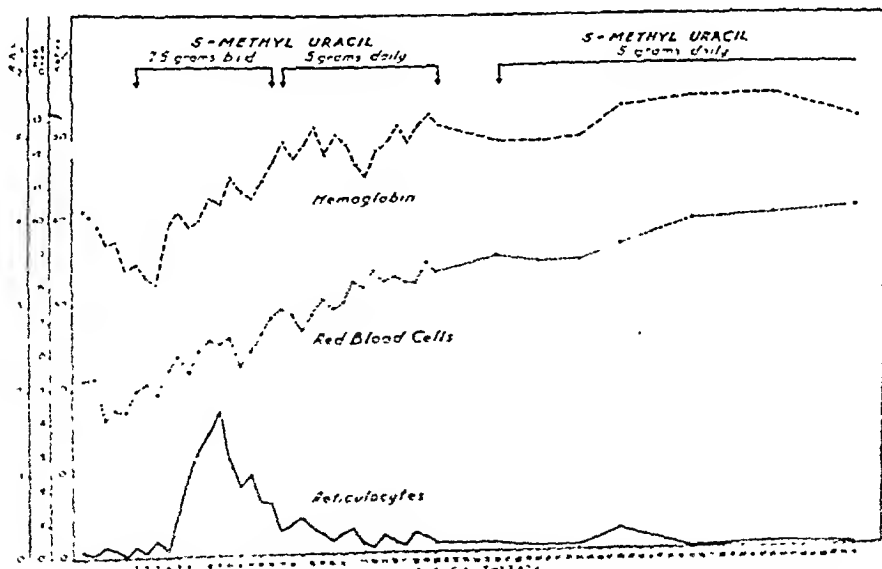


FIG. 4.—The effect of 5-methyl uracil on macrocytic anemia of tropical sprue.

was normoblastic and indistinguishable from the sternal bone marrow obtained from Case 3 at an analogous time during the latter's reticulocyte response to treatment with synthetic folic acid. After 8 days of treatment there was a striking increase in the patient's appetite. His tongue became normal subjectively, and there was temporary objective improvement; but both of these subsequently relapsed. His stools decreased to 1 a day, were dark brown in color, and tended to be normal in consistency although they were not well formed. By the 63rd day after treatment had been instituted, the red cell count was 4.03 million, and the hemoglobin was 13.7 gm. (89%). Therapy was maintained on this patient and a maximum erythrocyte count of 4.76 million was attained on the 139th day of treatment. The hemoglobin on that day was 12 gm. (78%). These figures are not included in Table 6 or in Figure 4. By this time the patient felt well and strong and had no subjective complaints.

Discussion. An analysis of Figure 1 brings out certain points of apparent difference in the hematologic responses of a patient with the macrocytic anemia of pernicious anemia in relapse who received concentrated liver extract, synthetic folic acid and synthetic 5-methyl uracil on 3 different occasions. At the time of administration of each of these substances, this patient's erythrocyte count was essentially the same. Because of this and because of the fact that his general condition at the time of each separate course of therapy was also essentially the same, it is reasonable to expect almost identical reticulocyte responses to each of these substances if they are equally hematologically effective. It is clearly evident that such identical responses were not obtained. The reticulocyte peak was highest with concentrated liver extract, next highest with folic acid, and lowest with 5-methyl uracil. Differences in rate of red cell rise are also evident. With concentrated liver extract as the therapeutic agent, there was an increase in erythrocytes of 3.69 million per c.mm. of peripheral blood in a 57 day period of time. This brought

the red blood count of Case 1 to 5.08 million. When synthetic folic acid was used as the therapeutic agent, there was a red cell increase of 3.33 million in a similar period of time (65 days). This rise brought the patient's red cell count to 4.97 million. When synthetic 5-methyl uracil was employed as the only form of anti-anemic therapy, the erythrocyte level reached a peak of 2.39 million in 21 days. This represented a net increase in red cells of 530,000. By the 60th day after therapy had been instituted, the patient had already relapsed. An analysis of the 3 clinical responses attained in Case 1 to each of the substances employed in therapy is a far more difficult matter. Upsurge in well-being is almost indescribable; yet it is a very definite and important reaction. This upsurge in well-being occurred at about the same time in Case 1 when either concentrated liver extract or synthetic folic acid was the therapeutic agent. In effect there is little noticeable difference in the time of its occurrence or degree of its magnitude when either of these substances is used. There is a noticeable and very definite lag period in the time of onset in this sign of improvement when 15 gm. of synthetic 5-methyl uracil is the sole therapeutic agent given daily. Using this substance, we have been impressed by the fact that this reaction usually occurs some 3 to 5 days later than it does with either folic acid or liver extract. In Case 1, however, the manifestations of an upsurge of well-being never occurred when 5-methyl uracil was administered. The symptoms referable to glossitis are more consistently relieved by concentrated liver extract and folic acid than by 5-methyl uracil in the dose given. It has been observed that there has been no change in the glossitis in several of our patients treated with this latter substance. An increase in appetite and disappearance of weakness occurred with the same rate of speed in Case 1 when either liver extract or folic acid was administered. Initially this patient showed a similar response to 5-methyl uracil, but soon the response was

lost. The symptoms referable to paresthesias are much more often relieved with concentrated liver extract than with either folic acid or 5-methyl uracil. In general it can be said that, with the use of either sufficient concentrated liver extract or sufficient synthetic folic acid, there occurred an almost identical clinical response and subsequent improvement in Case 1 but that the height of the reticulocyte response and the rate of the red cell rise was of a slightly lower order following the administration of folic acid than it was following concentrated liver extract therapy. Synthetic 5-methyl uracil effected a less dramatic clinical and hematologic response than did either concentrated liver extract or folic acid.

Figure 2 represents the hematologic response of Case 2 (nutritional macrocytic anemia) to these same 3 substances. The reticulocyte response to folic acid was tremendous, but the rate of red cell rise was definitely slower than it was with the use of concentrated liver extract in dosage described. When liver was administered for 15 days, there was an increase in erythrocytes of 4.92 million over a period of 58 days. When folic acid was given, the increase in erythrocytes was only 2.35 million over a 41 day period; and a count of 4 million red blood cells was never reached. The reticulocyte response and the rate of red cell rise following 5-methyl uracil therapy were both of a lower order than those obtained by the use of either of the other 2 substances. The clinical responses of this patient to these 3 substances in the doses given were of the same order and magnitude as discussed under Case 1.

A comparison of Figures 3 and 4 shows a less dramatic hematologic response to synthetic 5-methyl uracil than to synthetic folic acid in persons with the macrocytic anemia of tropical sprue. The delayed clinical response following the administration of 5-methyl uracil is obvious to those who have used both substances. Folic acid in some fashion acts very much as does liver extract in that there is some

indefinable general systemic effect which manifests itself as a generalized increase in strength or well-being or state of mind. Synthetic 5-methyl uracil does not have this function to the same degree at the dose level used by us.

The observed differences in the hematologic response to concentrated liver extract and synthetic folic acid are almost academic. The clinical response to folic acid is good, and it is almost identical with that of concentrated liver extract. However, for constancy and speed of reaction, concentrated liver extract is the more predictable of the 2 substances. The rate of red cell rise following folic acid therapy in these macrocytic anemias is somewhat slower than that which follows the administration of concentrated liver extract. Each substance has its advantage. Folic acid is easy to administer, and only small amounts by mouth are required for a very good response. Concentrated liver extract sometimes causes a more rapid increase in red cells. Synthetic 5-methyl uracil probably has no place in practical therapeutics. It has the distinct disadvantages of being effective only in very large amounts and of producing a clinical and hematologic response of a lower order than those effected by either concentrated liver extract or synthetic folic acid. Scientifically, however, 5-methyl uracil is of great importance. The authors are dubious that synthetic folic acid or synthetic 5-methyl uracil will prevent the development of the neural disturbances of Addisonian pernicious anemia.

These observations support the current idea that liver contains multiple anti-anemic substances. It is known that there is not enough folic acid in concentrated liver extract or crude liver extract to account for the activity of these various preparations. Obviously there is not enough 5-methyl uracil present. There still remains an unknown or a group of unknowns in liver which effect hemopoiesis. It is our opinion, and the opinion of others, that 5-methyl uracil may be converted into folic acid, possibly in the

intestinal tract, and in that manner cause maturation of red blood cells. This idea is not borne out by the substitution experiments of Stokes. How folic acid performs its function is as moot a question as that of how liver extract functions in such very small amounts. These are problems to be solved by the physiologists, biochemists and bacteriologists.

Summary and Conclusions. Comparative clinical and hematologic studies on the macrocytic anemia of pernicious anemia, of nutritional deficiency, and of tropical sprue, by the use of concentrated liver extract, synthetic folic acid, or synthetic 5-methyl uracil are presented. The points of difference in the clinical response, the reticulocytosis and rate of red cell rise following the administration of each of these 3 substances are discussed.

The hematologic findings show that under the conditions of the study and in the dosages used, each of these 3 sub-

stances causes a remission. The clinical and hematologic response to folic acid parallels that which occurs following concentrated liver extract therapy, but the rate of regeneration is greater with potent liver extract. We especially recommend folic acid where there is sensitivity to liver. Synthetic 5-methyl uracil is the least effective of the 3 substances. The rate of red cell rise and the peak attained is definitely of a lower order than that obtained with either synthetic folic acid or concentrated liver extract. While 5-methyl uracil is of great scientific interest, it has no practical therapeutic value at the dosage level required to maintain a normal red blood count. From these and other studies it seems to the authors that the active principle in liver extract is not folic acid but is a very powerful substance which, when obtained in pure form, probably will be no more efficacious per unit weight than is folic acid.

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CLINICAL SIGNIFICANCE OF HYPERBILIRUBINEMIA DUE TO NICOTINIC ACID

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VILLA⁵ on the basis of extensive clinical trial advocates nicotamide in the treatment of various types of liver dysfunction. This drug appears to produce a striking remission of jaundice, provided the liver damage has not reached the irreversible stage.

The effect of nicotinic acid on the bile excreting function of the liver is the subject of the present investigation. The results obtained fully support Villa's conclusions.

As shown by Mattei,⁴ 60 to 90 minutes after an intravenous injection of 30 mg. of sodium nicotinate, the level of the indirectly reacting serum bilirubin rises, remains high for 2 to 3 hours, and then drops slowly to normal in 6 to 8 hours (Fig. 1).

This technique is obviously valuable for investigating the function of the liver to excrete bile, since it acts as an endogenous bilirubin tolerance test. The cholemic effect of nicotinic acid seems to be specific, as several closely related substances (nicotamide, niketamide) as well as a number of compounds with similar pharmacological action (histamine, acetylcholine and epinephrine) appear to be inactive. Injections of histamine or epinephrine cause a change in the serum bilirubin level, but the rise is never higher than that observed during the normal diurnal fluctuation.

In studying the mechanism of the action of nicotinic acid, we also observed the behavior of serum chlorides, uric acid, erythrocytes and reticulocytes after the injection of this agent. Since these constituents were not significantly changed,

it appears fairly certain that nicotinic acid does not mobilize bile pigments from tissue reserve, nor cause an increase of the normal hemolytic process. It is, however, possible that nicotinic acid activates normal oxidative processes, since it is known, for instance, that coproporphyrin, which is present in large amounts in pellagra blood (Frontali¹), is strikingly diminished after nicotamide therapy. According to Kühnau,² nicotinic acid is important in the normal catabolism of blood pigments.

We have so far studied the bilirubin response to nicotinic acid in 42 patients with hepatic disease. These patients were also studied with other liver function tests following Watson's profile scheme.^{6,7} The results with the nicotinic acid test clearly show that the capacity of the liver to excrete bile is measured. When this function is deficient, the serum bilirubin level is still high after 8 hours, and directly reacting bilirubin is present in the blood.

In non-jaundiced patients in which the bilirubin level is elevated, the bilirubin curve is normal, showing that the function to excrete bile is unimpaired even when hepatic dysfunction of varying degree is indicated by other function tests.

A higher response to nicotinic acid is observed in jaundiced patients whether caused by infective hepatitis, obstruction, arsenical poisoning, cholangitis, or other factors. This is probably due to two factors: (1) the mobilization of pigments from the tissues into the blood stream, and (2) the elimination of this excessive bilirubin in the blood depending on the efficiency of the excretory function of the liver.

In cases involving only the first factor, a marked rise of total and directly reacting bilirubin is observed, but after 8 hours the level is back to normal, due to the efficiency of the liver to excrete pigments. Several diseases of the liver of which the recovery stage of infective hepatitis is typical show this type of curve (Fig. 2).

to rise after the 8th hour (Fig. 4). Conditions in which this was observed were obstruction from new growth and from calculi as well as in the early icteric stage of infective hepatitis.

It is worth recording the paradoxical effect we observed in a case of jaundice due to poisoning from parenteral arsenic.

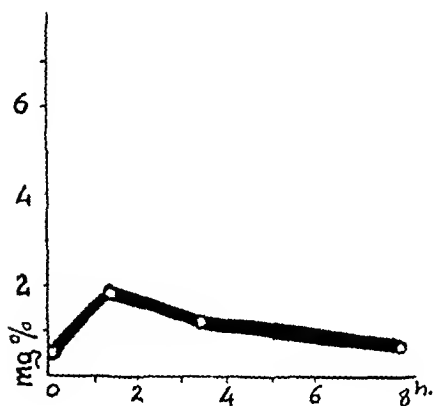


Fig. 1

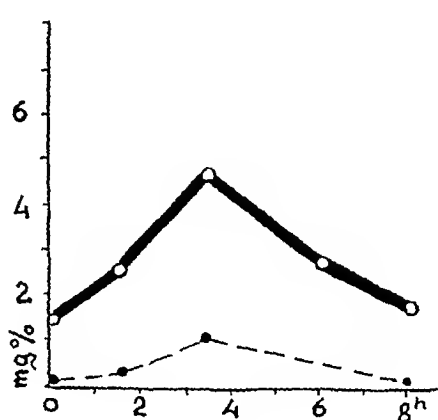


Fig. 2

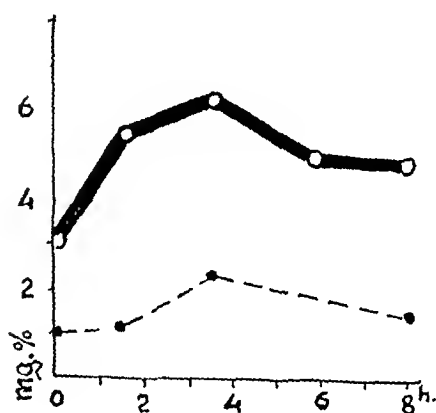


Fig. 3

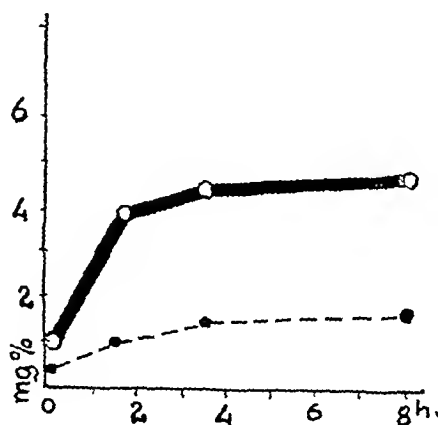


Fig. 4

— Total serum bilirubin

--- Direct reacting bilirubin

In cases involving a disturbance of the biliary excretion function, the level of both the total and the direct reacting bilirubin rises and remains high even after 8 hours (Fig. 3). If complete blockage of the bile excretion exists, the total and the direct reacting bilirubin levels continue

The total and direct acting bilirubin remained unchanged for the first 60 to 90 minutes, then dropped slowly to much lower levels. The rapid excretion of bilirubin, possibly due to the stimulation by nicotinic acid, is a satisfactory explanation and suggests why nicotinic acid has pro-

phytaetic and therapeutic activity in liver poisoning from drugs such as arsenobenzene.

Two of our observations clearly demonstrated that the behavior of serum bilirubin after nicotinic acid is strictly dependent on the capacity of the liver to excrete biliary pigments. In one patient suffering from jaundice of 5 months' duration due to chronic cholangitis, who underwent a cholecystostomy, the intravenous injection of nicotinic acid was followed by an increased excretion of bilirubin in the bile. It rose from 0.4 to 1.36 mg. per 100 cc. with the maximum at the third hour. In another patient, a case of infective hepatitis in the early stage, a curve of the type given in Fig. 4 was observed. After 5 days the test was repeated and found that the curve for bilirubin after nicotinic acid was normal which indicated that the biliary excretion of the liver was completely restored and suggests that this function is only temporarily depressed in infective hepatitis.

Summary. The serum bilirubin level was followed for 8 hours after the injection

of 30 mg. of sodium nicotinate in several types of liver disease to demonstrate experimentally the therapeutic value of this agent. In a normal subject, nicotinic acid causes a rise of the indirect reacting bilirubin level for 3 to 5 hours. Such an action is not observed when other substances similar to nicotinic acid, either in structure or pharmacological action, are injected. The test is strictly dependent on the liver's capacity to excrete bile. Cholesterol and bile salts do not generally follow the variations of bilirubin. The reason for this is still uncertain and is being further investigated.

In 42 patients the bilirubin curve was found not to be typical for any particular type of liver disease, but depended on the capacity of the liver to excrete bile pigments. When this function was impaired the serum bilirubin remained high and direct reacting bilirubin appeared.

In a patient with long standing jaundice who underwent a cholecystostomy a direct stimulation of the liver's function to excrete bile was demonstrated.

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ATYPICAL ANEMIA, WITH SPHEROCYTES AND TARGET CELLS COEXISTING IN THE BLOOD

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TARGET cells, studied in detail by Barrett,¹ are very thin cells which in stained films have a deeply staining center so that they look like a bullseye; because of their thinness, the volume-thickness ratio is large, so that they can absorb large volumes of fluid from hypotonic solutions before they rupture, that is, they have properties opposite to those of the spherocyte, and in particular they show decreased fragility. They are most evident in sickle cell anemia and in Cooley's erythroblastic anemia of childhood³ and its adult form,^{8,20,22} all of which show decreased red cell fragility, lysis being inappreciable at salt concentrations greater than 0.35% NaCl. Such cells are, however, common in other conditions, notably obstructive jaundice and iron deficiency anemia of color index below 0.6, and there show their resistance to lysis by hypotonic solutions quite clearly.

This case is presented because target cells and spherocytes coexisted in the blood, so that lysis of red cells was just appreciable in 0.60% NaCl, 50% complete in 0.335% NaCl, but incomplete in distilled water.

Case Report. A male office worker, aged 37, had always been in good health until in November 1944 he developed a cough and noticed that he was becoming pale and weak. He was admitted to Hertford County Hospital, where no disease was found in his lungs, but the liver was found palpable 2 inches below the costal margin. The spleen was not palpable. His hemoglobin was "55%" and "bizarre" changes were noted in the stained film. He remained in hospital for 6 weeks, receiving preparations of iron, vitamins and liver; during this period the hemo-

globin rose to "71%," but this appeared unrelated to treatment. In June 1945 he was referred to Dr. Geoffrey Evans at Cell Barnes Hospital (E. M. S.) for further investigation.

There was no family history of anemia; his sister and his 2 children had normal hemoglobin levels and showed no abnormalities in the stained film. His parents and grandparents were not related, and were to the best of his knowledge, of English country stock (without any admixture of Levantine blood). He complained only of weakness and lassitude, with shortness of breath on exertion. He slept poorly. He was a well-built man with a sallow, subicteric complexion, and had received in childhood a fracture of the nose to which he, and ourselves, attributed a slightly mongoloid appearance. There was moderate pallor of the mucosa, gross dental caries and pyorrhea alveolaris. The lungs were clear, the heart normal except for a localized apical systolic bruit. The liver was palpable 1½ inches below the costal margin, but the spleen was not clinically enlarged. There was no enlargement of lymph nodes, no leg ulcers, and no changes in the skull or in the long bones could be detected.

INVESTIGATIONS. *Radiologic:* long bones, skull and alimentary tract were normal; the spleen was enlarged to about twice its normal size; chest normal.

Chemical: gastric analysis was normal; stools contained no occult blood; urine contained excess urobilin.

Gastroscopy (G. W.) showed only extreme pallor of the mucosa; *sigmoidoscopy* (Dr. Evans), no abnormality found.

Blood and marrow (June 26, 1945): Hemoglobin, 52% (7.4 gm. per 100 cc.); erythrocytes, 3,600,000 per c.mm.; hematocrit, 27.6%; color index, 0.73; M.C.V., 77 cμ; M.C.H.C., 26.8%; M.C.H., 20.6 γγ; halom-

after reading, 8μ ; Price-Jones curve, mode 8μ , mean 7.12μ ; standard deviation, 1.29μ ; coefficient of variation, 18.15%; M.C.T., 1.38μ ; fragility (linear on arithmetic probability paper), from 0.6% NaCl (0.27% lysis) to 0.16% NaCl (96.8% lysis); a few cells intact in distilled water; M.C.F., 0.355% NaCl; standard deviation, 0.0875% NaCl (normal M.C.F., $0.422 \pm 0.0281\%$; standard deviation, $0.03025 \pm 0.00351\%$).¹⁰

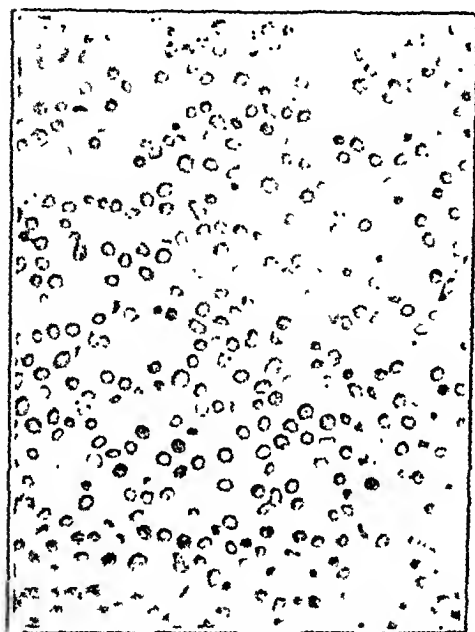


FIG. 1.—Peripheral blood, $\times 400$; Leishman's stain.

Leukoerythrocytes, 5300 per c.mm.; immature myeloid cells, 5% (including a few myeloblasts); mature neutrophils, 32.5%; eosinophils, 9.5%; lymphocytes, 43.5%; monocytes, 5.5%; plasma and Türk cells, 1%. Nucleated red cells, with small pyknotic nuclei and scanty, ragged, orthochromatic cytoplasm, were present; 95 to 1000 leukocytes (about 500 per c.mm.). The erythrocytes showed extreme anisocytosis, with some very small but few very large cells, poikilocytosis and anisochromia; many perry cells, target cells and spherocytes were present. Reticulocytes were scanty, never more than 1%; Howell-Jolly bodies were few and Cabot's rings were not seen. No sickling occurred in sealed preparations observed over a period of 48 hours. Grouping

(Dr. Mourant): A1, Rh1, Rh2; Coombs' test¹¹ for adsorbed globulin negative.

Bilirubin: direct reaction, negative; total, 0.8 mg. per 100 cc.; Wassermann and Kahn tests negative.

Sternal marrow (Nomenclature Scott¹²): cellularity increased; leuko-erythrogenetic ratio, 0.227; erythropoiesis normoblastic, granulopoiesis shows many "P.A. giant stabs." Count: reticulum cells, 1.4%; myeloblast, 3.2%; promyelocytes, 2.6%; neutrophils: myelocytes, 7.8%; juveniles, 3.8%; stabs, 2.6% (of which half were giant forms); segmented, 2%; eosinophils: myelocytes, 2.4%; others, 0.6%; basophil myelocytes, 0.2%; lymphocytes, 1%; plasma cells, 0.8%; monocytes, 0.2%; normoblasts: pronormoblast, 6%; basophilic, 11.6%; polychromatic, 37.4%; orthochromatic, 19.6%; unclassified, 1%. Mitoses: granular cells, 0.4%; erythroblasts, 2.2%.

Cytologic abnormalities were numerous and prominent, and were studied in Leishman and Feulgen smear preparations; among the granulocyte precursors there was nucleic acid starvation comparable with that seen in pernicious anemia,¹³ leading to the production of the tetraploid giant "stabs" once thought to be as characteristic for pernicious anemia as are the changes in the erythroblasts. Among the erythroblasts the outstanding feature was the breakdown of the normal spindle development and its replacement by abnormal multipolar spindles; of 100 mitoses, 55 were multipolar, 10 bipolar, and 35 unclassifiable because of clumping of the chromosomes. Many of the multipolar figures showed incomplete separation at anaphase, with persistent bridging leading to the restitution of a single, large (up to 16μ) distorted, hyperploid, resting nucleus; frequently micro-nuclei, derived from chromosomes which had become detached from the spindle, were also present, and a few cells containing up to 20 micro-nuclei were found. These last are presumably the product of a cell division in which many chromosomes became dissociated from the spindle and failed to constitute a daughter-nucleus. In addition, hypoploid mitoses were present, an occasional cell showing as few as a dozen chromosomes in a tri-polar mitosis. Cell division occurred mainly in cells corresponding to the "normoblast B" of Israels,¹⁵ well differentiated, with much heterochromatin,

and with polychromatic or orthochromatic cytoplasm.

PROGRESS. No definite diagnosis was made. The patient received iron (ferrous sulphate), parenteral liver extracts of known potency (Anahæmin, Plexan), and proteolyzed liver by mouth (Hepamino) and vitamin supplements, and his hemoglobin rose again to 71%. Col. A. M. Washburn, M.C.,

week he had become much worse and was dyspneic on the slightest exertion.

Studies now showed: Blood: hemoglobin, 38% (5.4 gm. per 100 cc.); erythrocytes, 2,500,000 per c.mm.; hematocrit, 21.5%; color index, 0.76; M.C.V., 86 μ ; M.C.H.C., 25%; leukocytes, 7400 per c.mm.; stained film, differential count and bilirubin showed little change.



FIG. 2.—Erythroblasts in bone marrow; Feulgen stain: A, multiple micronuclei, $\times 800$; B, anaphase bridge and multipolar spindle, $\times 950$; C, breakdown of spindle, $\times 950$.

A.U.S., kindly saw the patient with us, but was equally puzzled. Splenectomy was considered, in view of the evidence of increased hemolysis and of spherocytosis, but was postponed, and the patient discharged to remain under observation. On September 12 he was readmitted; during the previous

He did not improve after a weeks rest, and the rise in hemoglobin after a transfusion of 500 cc. blood was evanescent; he developed fever up to 99° , and purpuric spots appeared on his trunk. It was decided to perform splenectomy before his condition became critical. The operation was per-

formed by Mr. J. P. Hosford on October 2, after transfusion of 1000 cc. packed red cells, which raised the hemoglobin to 70%; a blood film taken during anesthesia showed about 1 mature normoblast to every 50 red corpuscles, or about 70,000 per cmm. The spleen, enlarged to twice the normal size, and a splenunculus about 1.5 cm. diameter, were removed, but 8 hours later, after recovery from the anesthetic, the patient collapsed with a feeble pulse (rate 120), and signs of collapse of the right lower lobe; he never recovered and died 4 hours later.



FIG. 3.—Giant "stab" neutrophils, $\times 800$; Feulgen light green.

AUTOPSY (G. D.) 12 hours after death: External: rigor mortis and hypostasis present; left-sided Kocher incision. Head and brain normal; mouth, gums retracted and infected, several carious stumps; tongue, thyroid, normal. Chest, pericardium contains 50 cc. straw-colored fluid; epicardial fat increased, ventricles dilated, myocardium fatty and friable, small subendocardial hemorrhages in wall of left ventricle; great vessels normal. Respiratory organs: diffuse tracheobronchitis with submucous hemorrhages, increasing in severity in the smaller bronchi; erosion of mucosa at end of endotracheal tube: patchy collapse of the lungs, involving whole right lung and left lower lobe, collapsed regions intensely engorged and edematous. Alimentary system normal.

Operation site: about 50 cc. blood as a firm clot over sutures, otherwise no blood in peritoneal cavity. Liver, 3 pounds 12 ounces pale. Suprarenals normal. Kidneys, left 7 ounces, right 6 ounces, cortex pale, otherwise normal. Femur, vertebrae, ribs, skull, all contain red marrow.

HISTOLOGY. Trachea: mucosal atrophy with hyperemia of submucosal vessels, some epithelial desquamation. Lungs: all vessels engorged; patchy collapse and compensatory emphysema and edema; the bronchioles contain a cellular mononuclear exudate and there is sloughing of their epithelium; in some areas an acellular exudate appeared to close the alveoli as in "rheumatic pneumonia." Heart: myocardium shows slight fatty change. Liver: definite increase in free iron, confined to the liver cells; bile pigment increased in the center of the lobules; the sinusoids are dilated and contain many erythroblasts, and the portal tracts are infiltrated with erythroblasts; definite myeloid metaplasia. Kidney: recent cortical necrosis; in the pelvic fat there is a focus with the structure of bone marrow, though no bone is present; the predominating cell is an erythroblast; there is no excess of free iron. Pancreas and testis, normal. Bone marrow: hyperplastic, the predominating cell being an immature polychromatic normoblast, but granular cells are common. Spleen: there is a considerable increase in free iron, both in macrophages and in the tissue of the pulp, and an increase in the fibrous tissue; the pulp is packed with blood containing many erythroblasts, and there is some myeloid metaplasia, most marked in the splenunculus; there is some erythrophagocytosis, but this is not a prominent feature. Lymph nodes; the general architecture is preserved; the sinuses are packed with blood containing erythroblasts, but there is no true myeloid metaplasia. Anatomic diagnosis: pneumonia (virus type), cortical necrosis of the kidney, hyperplasia of bone marrow with myeloid metaplasia in liver, spleen and renal pelvic fat.

Discussion. The anatomic changes in this patient are not specific, but are common to many types of anemia in man, and to some syndromes in animals; it differs from pernicious anemia only in the normoblastic type of erythropoiesis and

in the focus of erythropoiesis in the renal pelvic fat. For this reason, study of the peripheral blood and of the cytopoiesis of the red cell is more likely to prove fruitful than is the classic histologic approach; it is obvious that details of cell

structure can be studied more satisfactorily in smears of cells dissociated from their surroundings and suitably treated, rather than in sections, where the cell retains the roughly spherical shape it had when living.

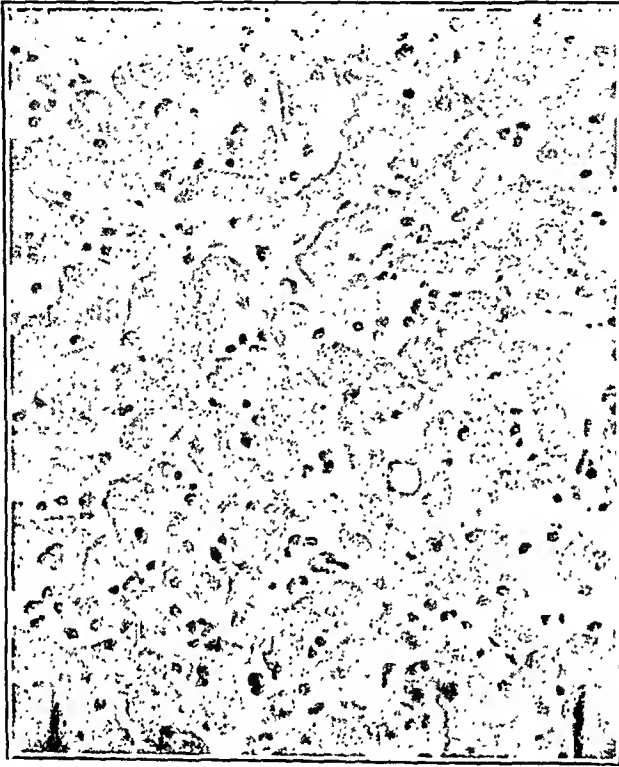


FIG. 4.—Liver, $\times 300$; Barratt's stain.

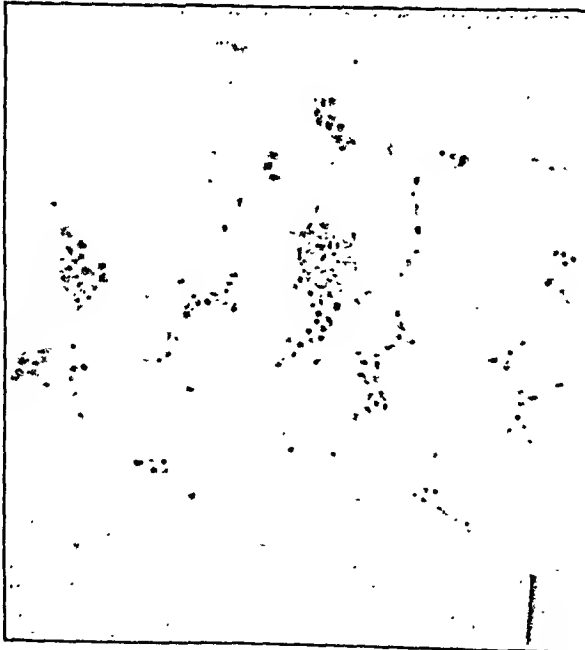


FIG. 5.—Renal pelvic fat, $\times 150$; Barratt's stain.

CYTOLOGY. The changes in this patient are not unlike those described in pernicious anemia by La Cour,¹¹ but differ in that cell division is proceeding in a much more mature cell; in pernicious anemia division occurs chiefly at the promegaloblast and megaloblast "A" stage, and is comparatively rare in more mature cells; a much larger proportion of the multipolar mitoses of pernicious anemia appear to yield good, though hypoploid, cells. There can be no doubt that this patient suffered from some condition which was not pernicious anemia, for the resting nuclei differed markedly from those of any pernicious anemia marrow yet seen, whether in relapse or in remission: it was normoblastic, not megaloblastic, using the terms in the same way as Ferrata,¹² and Israels,¹³ but the normoblasts were abnormal. Several cases of hemolytic anemia, congenital and acquired, have been examined critically, but these show only very rare multipolar spindles, or anaphase bridging. The essential lesion appears to be the breakdown of spindle formation, yielding hyper- and hypoploid cells which undergo denudation to yield red corpuscles that vary extremely not only in diameter but also in thickness.

The presence of micronuclei in this case led one to compare them with the Howell-Jolly bodies so common in pernicious and hemolytic anemia. Both are Feulgen positive, and hence composed largely of deoxyribose nucleic acid; they are sharply defined, unlike the nucleic acid shed from the nucleus under the influence of irradiation or of cytotoxic agents, and so presumably have some inner structure. In material in which Howell-Jolly bodies are common in the peripheral blood, the bone marrow shows similar bodies in the cytoplasm of nucleated red cells, while the mitotic figures of these cells show occasional telophases in which a single chromosome remains between the 2 groups of chromosomes, either exactly midway between, or else towards the margin of the cell, well outside the region of the spindle. One is forced to the conclusion that these

bodies are not "nuclear remnants," but chromosomes dissociated from the spindle. In most cases this occurs in an almost mature cell, in which spiralization of the chromosome fiber (chromonema) is complete or excessive, so that the chromosomes are almost spherical and homogeneous; in less mature cells the chromonema is more extended and the resulting body may appear heterogeneous.

CLINICAL. *Differential Diagnosis.* Initially this patient was thought to be suffering from familial acholuric jaundice which had become clinically evident during adult life. Such cases are not rare, and the absence of clinical splenomegaly is not significant, for we have seen 3 patients with grossly enlarged spleens (1 with myeloid leukemia) which could not be detected at the bedside; this occurs when the spleen is adherent to, or pressed up against, the cupola of the diaphragm.⁴ The spherocytosis favored this diagnosis, though it is not, of course, pathognomonic of the condition,⁷ but the absence of reticulocytosis and the extremely wide range of fragility rendered the diagnosis untenable. For similar reasons the ordinary acquired hemolytic anemias could be excluded, for erythroblastemia of significant degree occurs only during, or just after a hemolytic crisis. Target cells were reported as a prominent feature in 1 case,¹⁹ but this showed reticulocytosis and atypical agglutinins in the serum.

The adult form of Cooley's Mediterranean anemia is familial, and occurs almost exclusively in persons of Levantine origin, especially in the offspring of cousin marriages. In favor of this diagnosis were the presence of target cells and erythroblasts, hepato- and splenomegaly; but the patient was of pure English origin, his parents were not related, and none of the 3 siblings was affected; while spherocytes do not occur in this. This diagnosis also was discarded.

A leuko-erythroblastic reaction to marrow deposits of carcinoma, lymphadenoma, or to tuberculosis of the spleen could at once be discarded, as could the erythro-

blastemia of chronic malaria, stated¹⁷ to be particularly common in Algeria; in this infection splenomegaly is considerable, and also our patient had never left England.

The condition bears little resemblance to the acute erythremia of Di Guglielmo,⁹ but differs comparatively little on the clinical side from the 1 case of Israels¹⁴ which was less acute. It is not unlike the erythroblastosis of fowls,¹¹ which can manifest itself in all grades of severity.

One must conclude either that this is a new syndrome, and that further cases will be recognized, or that it is an "individual" response to some stimulus, comparable with the "acute erythromyelosis" of Garnier,¹³ with 35,000 erythroblasts per c.mm., 6% of which were in mitosis, which recovered in a month on treatment with liver extract. The only excuse for presenting single cases is that others may profit

by our observations, define the syndrome and develop a satisfactory treatment.

One final point: usually erythroblastemia is associated with reticulocytosis, though the 2 responses do not necessarily run parallel. Pittaluga,¹⁸ however, insists that "regenerative reticulocytosis has nothing to do with pathologic erythroblastosis," a rather surprising conclusion with which we are forced to agree.

Summary. 1. A patient suffering from an obscure anemia which failed to respond to treatment and terminated fatally after splenectomy is described.

2. This anemia is characterized by: (a) great variation in the resistance of the red corpuscles to lysis by hypotonic saline, manifested morphologically by the co-existence of target cells and spherocytes; and (b) breakdown of spindle development in partly differentiated erythroblasts.

3. This appears to be a hitherto undescribed syndrome.

We wish to thank Dr. Geoffrey Evans for permission to publish this case, and Mr. L. F. La Cour of the John Innes Horticultural Institute, who has advised us on the interpretation of the cytologic abnormalities and taken some of the photographs.

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NITROGEN BALANCE AND BLOOD VOLUME STUDIES IN MAN DURING AND FOLLOWING REPEATED PLASMA TRANSFUSIONS*

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BECAUSE of the wide use of plasma in the treatment of shock, and in certain cases of hypoproteinemia, there has been an increased interest in the fate or utilization of the plasma proteins. Elman¹¹ reviewed the literature up to 1943 and concluded that nitrogen balance can be maintained with plasma as the sole source of protein, providing the plasma employed causes no serious reactions. There is some controversy on this point, however, as the results of the nitrogen balance studies following intravenous infusion of plasma as reported by different laboratories have been at variance. It does not seem that these differences can be entirely explained by reactions to the injected plasma. Most of this work has been carried out on dogs which have received injections of dog plasma. Hegsted, Hay and Stare¹⁷ have found through growth studies in rats that human albumin is deficient in isoleucine and tryptophane. However, they demonstrated that oral feeding of this protein maintained nitrogen balance in adult dogs. These species differences in the requirements of specific amino acids make it difficult to reach any satisfactory conclusion on the fate of human plasma injected in human beings from animal experiments.

Excluding conditions of shock, or the first several weeks following a burn or fracture, when nitrogen excretion is known to be increased above the normal,^{18,20} there seem to be only 3 reports on nitrogen balance when human plasma was transfused into apparently normal individuals. Kreman, Hall, Kosehnitzke, Stevens and Wangenstein,²¹ and Wangenstein, Hall, Kreman and Stevens²² compared the use of human plasma with bovine plasma, and Muether and Andrews²³ reported some studies on 6 patients in conjunction with methods of preserving blood. None of these studies in humans included the alterations in plasma volume or hematocrit which resulted from the transfusion. Although there is information on such changes immediately, or a few days following a single transfusion,^{15,16,28} there are no reports on such alterations in the late post-transfusion period following repeated injections of plasma. The following study was, therefore, undertaken to obtain more information on the effect of human plasma transfusions on the nitrogen balance in man, and on changes in plasma volume, plasma proteins and hematocrit.

* This work was carried out in part under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and Wayne University. It was also supported in part by a grant from the Theodore A. McGraw Fund.

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Procedure. Three patients were selected for this study who seemed to be in a good state of nutrition.* Their case histories and detailed dietary management are given in the protocol. The following synthetic diet was fed in amounts to insure slightly greater than an adequate protein and caloric intake: Hydrolyzed casein (Amigen) dextro-maltose and orange juice supplemented with vitamins. Iron was contained in the diet in amounts almost equal to the accepted daily requirements (15 mg.), and additional amounts were given in the form of iron citrate in the last 2 subjects.

The patients received the diet for at least 4 days, and then nitrogen balance studies were carried out for two 4 day periods on this diet. Following this, protein was omitted from the diet for 5 days and in its place the patient was given a daily intravenous injection of plasma estimated to contain the same amount of protein as he had eaten on each of the previous days. (Amount for each patient given in the protocol.) Subsequently the patients were returned to their control synthetic diet and studied for from two to four 4 day periods. In the last 2 subjects, following the completion of 4 periods after the transfusion period, another 5 day period was added in which the protein in the diet was entirely eliminated in order to study the nitrogen excretion and partition under these conditions. This period was essentially the same as the third period when plasma was administered except that the patient was not given any parenteral protein.

Food, feces and urine were analyzed for total nitrogen content, and the following nitrogen constituents of the urine were determined: urea, ammonia, uric acid, creatinine, creatine and amino acids. The methods for these determinations have been described elsewhere.³³ Plasma volume, hematocrit, plasma protein and albumin determinations were made during the control period, and 18 to 20 hours following the last transfusion. In the first subject these same studies were also made on the 9th day after the last transfusion; in the second subject, on the 12th and 23rd day, and in the third subject, on the 9th and 24th day. The method for these determinations was essentially the same as that previously employed.¹

* Because of variation in age, nutritional state, etc., these cases were admittedly not ideal, but under the circumstances were the best that could be obtained.

Ten cc. of Evans blue dye (T-1824) containing 1 mg. per cc. were injected intravenously for the determination of the plasma volume. The total red cell mass was calculated from the plasma volume and hematocrit and while this method does not give reliable values,¹⁴ it was felt that the percentage changes in the total red cell mass might be of some significance.

Results. The data on nitrogen balance and urinary nitrogen partition are summarized in Tables 1 and 2. All 3 subjects were in positive nitrogen balance during the first 2 periods while receiving the hydrolyzed protein by mouth, except for Subject C. S., who showed an insignificant loss during the first period. This confirms the reports^{6,30} that hydrolyzed protein given orally will maintain nitrogen balance. During the 5 day period of plasma transfusion, all subjects were not only in positive balance, but the nitrogen retention during this period (particularly in Subjects J. M. and C. S.) was much greater than when nitrogen was fed in the form of casein hydrolysate. However, following the transfusion, the excretion of urinary nitrogen was increased over the control periods in all 3 subjects, although the retained nitrogen was not entirely lost. In the first subject, J. M., this resulted in only a slight loss, a total of 3.12 gm. in 8 days, or 13% of the amount gained (24.35 gm.) during the period of transfusion. However, in C. S., this loss was more marked, totalling 26.13 gm. in 9 days, or 85% of the amount gained (30.70 gm.). Subject C. M. lost a total of 7.68 gm. in 5 days, or 52% of the amount gained (14.90 gm.) during the transfusion period.

The urinary nitrogen excretion in the last 2 subjects on the protein-free diet was similar to that observed during the period of transfusion. The average nitrogen excretion in Subjects C. S. and C. M. during the periods of transfusion was 5 and 5.26 gm. respectively, whereas on the nitrogen-free diet it was 4.29 and 4.84 gm.

TABLE 1.—DATA ON NITROGEN BALANCE

TABLE II—DATA ON NITROGEN BALANCE									
Case	Period	N intake		N output			Nitrogen balance (gm.)	Body weight (kg.)	
		Amigen (gm.)	Orange juice (gm.)	Urine (gm.)	Feces (gm.)	Excreta (gm.)			
J. M.	1	13.43	0.37	12.50	0.61	..	0.69	62.0	
	2	(11.42) (11.85) (11.26) (12.19)	
	3	13.43	0.38	Av. 11.68 (8.54) (6.21) (5.31) (6.53) (5.25)	1.12	..	1.01	..	
	4	11.65*	0.49	Av. 6.37 (12.82) (13.02) (14.15) (14.36)	0.77	0.13	1.87	..	
	5	13.43	0.48	Av. 13.59	0.75	0.01	-0.47	64.4	
	6	13.43	0.41	13.53	0.65	..	-0.31	63.1	
	1	9.74	0.26	9.10	1.18	..	-0.28	59.8	
	2	9.74	0.29	8.88	0.78	..	0.37	59.8	
	3	(6.93) (4.21) (4.59) (4.84) (4.43)	
	4	11.70*	0.31	Av. 5.00 (9.00) (14.29) (13.67) (12.75)	0.87	..	6.14	59.3	
	5	7.96†	0.21	Av. 12.43	0.89	0.02	-5.17	59.5	
	6	9.95	0.22	10.70	0.56	..	-1.09	60.8	
	7	9.74	0.27	8.97	0.78	..	0.26	60.0	
	8	9.74	0.25	8.91	0.31	..	0.77	..	
9	9.35 (9.14) (4.95) (3.64) (3.45) (3.03)	0.56	..	0.08	60.0		
C. S.	1	..	0.24	Av. 4.84	0.47	..	-5.07	59.4	
	2	11.30	0.55	8.43 (10.26) (8.92) (7.48) (8.20) (8.31)	1.28	0.01	2.13	67.1	
	3	11.30	0.50	Av. 8.63 (5.93) (4.51) (4.27) (5.58) (6.38)	0.57	0.14	2.46	67.2	
	4	8.13*	1.07	Av. 5.33 (10.72) (15.43) (14.22) (12.93)	0.77	0.12	2.98	..	
	5	11.30	0.46	Av. 13.33	0.29	0.06	-1.92	..	
	6	11.30	0.43	10.31	0.80	0.01	0.61	..	
	7	11.30	0.47	8.66	1.05	0.30	1.76	..	
	8	11.30	0.46	8.27	0.78†	..	2.71	..	
	9	..	0.44	4.29	0.68	..	-4.53	..	
	C. M.	1	..	0.24	Av. 4.84	0.47	..	-5.07	59.4
		2	11.30	0.55	8.43 (10.26) (8.92) (7.48) (8.20) (8.31)	1.28	0.01	2.13	67.1
		3	11.30	0.50	Av. 8.63 (5.93) (4.51) (4.27) (5.58) (6.38)	0.57	0.14	2.46	67.2
		4	8.13*	1.07	Av. 5.33 (10.72) (15.43) (14.22) (12.93)	0.77	0.12	2.98	..
		5	11.30	0.46	Av. 13.33	0.29	0.06	-1.92	..
6		11.30	0.43	10.31	0.80	0.01	0.61	..	
7		11.30	0.47	8.66	1.05	0.30	1.76	..	
8		11.30	0.46	8.27	0.78†	..	2.71	..	
9		..	0.44	4.29	0.68	..	-4.53	..	

During the period of transfusion and the nitrogen-free diet these 2 subjects showed an increase in % uric acid, creatinine and creatine excretion. Similar alterations were observed in the first subject during the transfusion period. However, the absolute amount of these various fractions was relatively constant, except for creatine excretion which was markedly increased in the first subject (J. M.) during the period of transfusion and in the last subject (C. M.) in the period following transfusion. The % urea nitrogen excretion was lower in this patient during transfusion and on the nitrogen-free diet. It was also lower on the nitrogen-free diet

(16%) but the value increased by the 12th day (24%) and returned to normal on the 23rd day. Subject C. M. showed no significant change on the 1st day following the last transfusion, but as in Subject C. S. showed an increase (16%) on the 12th day; on the 23rd day the value was 10% above the control.

Hematocrit values were decreased during and following the period of injection. In the first subject, J. M., the fall in the hematocrit appears to be largely the result of dilution rather than decrease in the volume of circulating red cells. But in the last 2 cases (C. S. and C. M.) the drop in hematocrit was marked and cannot be

TABLE 2.—URINARY NITROGEN PARTITION

Case	Period	Urea		Ammonia		Uric acid		Creatine		Creatinine		Amino acid		Partition nitrogen % of Kjeldahl nitrogen
		Mg.	%	Mg.	%	Mg.	%	Mg.	%	Mg.	%	Mg.	%	
J. M.	2	9,722	83.2	476	4.1	180	1.5	13	0.1	425	3.6	788	6.7	99.2
	3	5,115	80.2	152	2.4	179	2.8	178	2.8	422	6.6	456	7.2	102.0
	4	11,306	83.2	475	3.5	250	1.8	92	0.7	422	3.1	953	7.0	99.3
	5	11,223	82.9	613	4.5	236	1.7	21	0.2	415	3.1	820	6.1	98.5
C. S.	1	7,257	79.7	504	5.5	196	2.2	14	0.2	334	3.7	418	4.6	95.9
	2	7,584	85.3	414	4.7	190	2.1	39	0.4	338	3.8	374	4.2	100.5
	3	4,233	85.0	196	3.9	142	2.8	35	0.7	321	6.4	275	5.5	104.3
	4	11,362	91.4	302	2.4	193	1.6	60	0.5	334	2.7	522	4.2	102.8
	5	9,014	84.2	450	4.2	210	2.0	55	0.5	337	3.1			
	6	7,595	84.6	459	5.1	200	2.2	55	0.6	340	3.8	452	5.0	101.3
	7	7,740	86.9	348	3.9	211	2.4	43	0.5	331	3.7	492	5.5	102.9
	8	8,236	88.0	307	3.3	146	1.6	50	0.5	323	3.4	426	4.6	101.4
	9	3,849	79.4	280	5.8	175	4.0	33	0.7	481	9.9	235	4.8	104.6
C. M.	1	6,742	80.0	524	6.2	130	1.5	36	0.4	622	7.4	523	6.2	101.7
	2	7,077	82.0	306	3.5	161	1.9	65	0.8	602	7.0	605	7.0	102.2
	3	4,139	77.6	213	4.0	199	3.7	77	1.4	529	9.9	499	9.3	105.9
	4	11,215	84.1	464	3.5	206	1.5	142	1.0	584	4.4	823	6.2	100.7
	5	8,840	85.7	598	5.8	184	1.8	67	0.6	483	4.7	619	6.0	104.6
	6	7,280	84.0	365	4.2	204	2.4	8	0.1	511	5.9	595	6.9	103.5
	7	6,596	79.8	436	5.3	179	2.2	44	0.5	565	6.8	793	9.6	104.2
	8	2,646	61.7	340	7.9	138	3.2	54	1.2	558	13.0	426	9.9	96.9

in the second subject (C. S.) but not during the period of transfusion. The decrease in % urea nitrogen excretion in the first subject (J. M.) during the transfusion seems insignificant. Ammonia and amino acid nitrogen excretion showed no marked alterations during the study.

As shown in Table 3, the changes in plasma volume following the transfusion were not consistent, but the trend was towards an increase. The first subject, J. M., showed a significant rise (38%) on the 1st day following the 5 days of transfusion, and the value was 11% above the control on the 9th day. The second patient (C. S.) showed only a small increase

accounted for by dilution. On the 12th day the calculated volume of circulating red cells was 31 and 36% respectively below the control value in these 2 subjects. It was at least 23 days before the hematocrit and volume of circulating red cells approached the control value.

Protein concentration in the first subject showed only slight changes during the entire experiment, but Subjects C. S. and C. M. both showed an increase in the plasma protein concentration following the periods of transfusion. Alterations in albumin-globulin ratios were small, except in C. M. where the ratio was consistently higher than the control value.

Total circulating protein immediately following the transfusion was increased (33 and 52%) above the control value, but as shown in Table 4 the increase was small compared to the amount of protein injected during the 5 days.

average of 5.56% protein. The transfusion was given in 2 divided doses, morning and evening. The diet during this time contributed 2076 Cal.

The temperature of the patient was normal previous to the transfusion. He had a chill on the 1st day and the transfusion had

TABLE 3.—PLASMA VOLUME, PROTEIN AND HEMATOCRIT CHANGES

Case	Day of transfusion	Days following last transfusion (Control)	Plasma volume change (%) (3171)	Hematocrit change (%) (43.4)	Blood volume change (%) (5602)	Circulating red cell mass change (%) (2131)	Protein concentration (%) 7.42	Total circulating protein change (%) (235)	A/G ratio 1.32
J. M.	4	1	+38	-10	+21	-2	7.96	+34	1.46
		3	..	-15	7.16	..	1.26
		8	..	-13	7.40	..	1.34
		9	+11	-11	+3	-8	6.79	+2	1.32
C. S.	3	(Control)	(2970)	(40.4)	(1983)	(2013)	6.37	(189)	1.47
		1	+16	-29	-3	-31	7.66	+52	1.52
		4	..	-39	8.52	..	1.16
		5	..	-46	8.52	..	1.41
		12	+21	-32	+2	-31	6.46	+38	2.00
		23	+4	-16	-6	-21	6.83	+5	1.73
		30	..	+9	6.72	(195)	1.43
C. M.	..	(Control)	(2902)	(46.9)	(5465)	(2563)	8.78	+36	2.24
		1	+4	-12	-6	-18	7.09	+22	2.12
		9	+16	-30	-9	-36	6.55	+7	2.66
		14	..	-17
		21	+10	-9	+2	-8

TABLE 4.—DIFFERENCE BETWEEN PROTEIN INJECTED AND INCREASE IN PLASMA PROTEIN

	Total circulating proteins		Increase (gm.)	Protein injected (gm.)	Difference between protein injected and increase in circulating protein (%)
	Before transfusion (gm.)	After transfusion*			
J. M.	235	314	79	364	22
C. S.	189	287	98	366	27
C. M.	195	265	70	254	28

* 18 to 24 hours after last transfusion.

Case Histories. CASE 1. J. M., 65 year old white man, admitted to the hospital because of bilateral hernia. Right herniorrhaphy done on April 11, 1944, and left on April 25. Convalescence from operations entirely uneventful.

On May 5, patient was started on diet consisting of 109.2 gm. hydrolyzed protein, 473 gm. dextro-maltose, 500 cc. orange juice, 2 gm. salt mixture, 100 mg. ascorbic acid, 20 mg. thiamin, 50 mg. nicotinic acid, percomorphum 4 minims, made up in 1000 cc. of water. This diet provided 86 gm. of protein and 2440 Cal. The first collection period was started on May 10. During the 3rd period the patient received the following amounts of plasma on 5 successive days: 1340, 1100, 1305, 1480 and 1320 cc. The plasma was obtained from the Receiving Hospital Blood Bank and contained an

to be temporarily stopped. He showed a urticaria on the 2nd day, and again had a chill on the 3rd and last day of transfusion. During this period of transfusion, the temperature ranged from normal to 101° F. He complained frequently of headache and some soreness in his mouth. He also complained of feeling nauseated and vomited 3 to 4 times.

Following the period of transfusion, his temperature was normal for the 9 days he was observed.

CASE 2. C. S., 67 year old white man, admitted and operated on, April 26, 1944, because of perforated gastric ulcer (perforation occurred 4 to 5 hours previous to operation). On May 7, the patient had a left saphenous ligation.

On May 31, the patient was started on a diet consisting of hydrolyzed protein

79.2 gm., dextro-maltose 435 gm., orange juice 300 cc., ascorbic acid 200 mg., thiamin 4.5 mg., riboflavin 2 mg., niacin 40 mg., percomorphum 5 ggts., and ferric ammonium citrate 15 cc. of a 25% solution made up in 750 cc. of water. This diet provided 62 gm. of protein and 2107 Cal. The first collection period was started on June 5. During the 3rd period the patient received 1000 cc. of plasma daily, obtained from Sharpe & Dohme, which contained 7.31% protein. The plasma was administered in 2 doses morning and afternoon. The diet during this time contributed 1817 Cal.

The temperature of the patient showed little fluctuation previous to the experiment and was normal 15 days before the study. The temperature remained normal throughout the entire experiment, except on the last day of the transfusion when it rose to 100° F. for a few hours, but it rapidly returned to normal and remained so.

The patient complained of some headache and towards the end of the 3rd period, of nausea and sore gums. He vomited following the very last transfusion. However, only 0.18 gm. of nitrogen were lost by this emesis. Through an error, this subject was not given the hydrolyzed protein on the 1st day following the transfusion, which explains the lower nitrogen intake in Period 4. No untoward symptoms were noted in the patient during the remainder of the experiment (27 days).

CASE 3. C. M., 20 year old Negro male, admitted to hospital and operated on, July 20, 1944, because of perforated duodenal ulcer (perforation occurred about 5 hours previous to operation).

Patient was started on a diet, August 4, consisting of 90 gm. of hydrolyzed protein, dextromaltose 539 gm., orange juice 600 cc., ascorbic acid 100 mg., thiamin 5 mg., riboflavin 3 mg., niacin 20 mg., pantothenic acid 25 mg., percomorphum 5 ggts., ferric ammonium citrate 15 cc. a 25% solution. The diet was made up in 750 cc. of water. The 1st collection period was started on August 8. The diet provided 70 gm. of protein and 2682 Cal. During the 3rd period the patient received 1000 cc. of plasma for 4 days and 500 cc. on the 5th. The last 500 cc. were omitted since the patient was not feeling well because of the frequent large transfusions. The plasma was obtained from Sharpe & Dohme, which

contained 7.31% protein. The plasma was administered in 2 doses, morning and afternoon. The diet during this time contributed 2344 Cal.

The patient had an elevated temperature (between 99.4 to 101.2° F.) for 60 hours after the operation and from this time until studies were begun his temperature was normal. During the period of transfusion his temperature was normal most of the time, but on several occasions rose to 100° F. He complained of headache, nausea, vomited small amounts several times and also complained of sore gums and throat. During the 1st post-transfusion period his temperature was normal most of the time, except for 2 rises to 100° F. The temperature remained normal during the remainder of the experiment (20 days) and no untoward symptoms were noted.

Discussion. *Nitrogen Balance Studies.* Although all subjects were in positive nitrogen balance during the period of transfusion, the urinary nitrogen excretion in the post-transfusion period was increased above the 2 control periods, resulting in a loss of nitrogen. The total urinary nitrogen excretion in the post-transfusion period was very similar for the 3 subjects, but the resulting nitrogen loss was variable. This difference may have been influenced by the age of this group which varied from 20 to 67 years. Subject C. M. showed a fairly marked positive nitrogen balance previous to the transfusion which might be accounted for by the fact that the study in this individual was started 2 weeks following the operation for perforated ulcer. It seems probable that the patient was still in the recovery or anabolic phase, and this could have influenced his response to the plasma transfusion. The difference in the nitrogen intake might also account for the variation in the loss of nitrogen in the 3 subjects following the transfusion. There is some evidence that the nitrogen balance during or following transfusion may be influenced by reaction to the injected plasma, and amount of plasma transfused. The results of the present study will, therefore, be discussed under these topics.

Positive nitrogen balance during periods of plasma transfusion have been reported by various workers,^{3,7,9,19,21,22,25,26,32} and in these cases no evidence of a reaction was noted. However, a negative balance in 1 experiment during the intravenous administration of plasma was reported⁷ in an animal that manifested a reaction to the transfusion. An increased nitrogen excretion in the post-transfusion period was noted²⁶ in 1 dog which reacted unfavorably to horse serum and in another animal which showed symptoms of irritation from the intraperitoneal injections of plasma. In the present study, Subject J. M., as shown in the case history, had chills, fever and some urticaria during the period of transfusion. He showed a marked increase in creatine excretion which was also noted by Daft, Robscheit-Robbins and Whipple⁷ in an animal that exhibited a reaction. Subject J. M. excreted on an average 1 gm. of nitrogen per day more than the other 2 subjects during the transfusion period. Excretion during this period may have been less and hence nitrogen retention greater had there been no reaction. Subjects C. S. and C. M. showed only minor and infrequent temperature elevations. Creatine excretion in Subject C. M. was increased in the post-transfusion period; no change in this constituent was observed in Subject C. S. Although no studies were made, it was observed that the blood pigments in the plasma were increased during and immediately following the period of transfusion, especially in these 2 subjects. Urinary nitrogen excretion during the period of transfusion was slightly higher in these 2 patients than during the time they were on the nitrogen-free diet. Since other studies^{7,19,21,22,32} in which the subjects were fasted or on a nitrogen-free diet showed little or no increased excretion during the period of transfusion, the nitrogen excretion observed in C. S. and C. M. may have reached a lower level had there been no undesirable effects from the transfused plasma. All 3 patients complained of

nausea, headache, and a sore mouth during the period of transfusion which subsided shortly thereafter.

It has been suggested⁷ that a sufficient amount of fat and carbohydrate may be necessary for the utilization of large amounts of plasma given by vein. An increased nitrogen excretion during transfusion and a few days following was reported⁷ in an animal that received 50 gm. of extrose as the sole source of calories. When this was replaced by 200 gm. of the Cowgill diet there was clinical improvement and the nitrogen excretion decreased. Although the subjects in the present experiment received no fat, caloric intake was calculated to be adequate (1800 to 2300 Cal. during transfusion period).

The first subject, J. M., received plasma from the hospital blood bank, whereas reconstituted lyophilized plasma* was used for the last 2 subjects. Dounce and Howland⁸ found that when crystalline beef liver catalase had been dried by the lyophilized process that it was not crystallizable, possessed about one-third the activity of the undried material, and that its hematin iron could be reduced, indicating some change in molecular structure. It has also been reported³¹ that there is a loss in clot strength of dehydrated plasma. Seegers²⁷ noted that the activity of thrombin was reduced after lyophilization. Although there is no direct evidence, it seems possible that the process of lyophilizing may alter the nature of the plasma proteins, and thus may have affected the nitrogen balance.

Elman and Davey,⁹ from their work in dogs, suggest that the quantity of plasma injected may have an influence on the utilization of the plasma protein. In their study, most of the gain in nitrogen during the week of injection was lost in the post-transfusion period. Their injections (600 cc. per day, or an amount equivalent to 7 gm. of nitrogen) were larger than those used by other workers. In a later study these same authors,¹⁰ from

* Kindly furnished by Sharpe & Dolme Co., Philadelphia, Pa.

work on intravenous administration of amino acids, concluded that there seems to be a ceiling utilization of nitrogen at least when given in this form. It seems plausible that there may also be a ceiling utilization of injected plasma protein. In the plasma transfusion studies on humans²¹ 500 cc. of plasma were injected daily for 5 days. Muether and Andrews²⁵ do not state the amount of plasma injected, but their figures of 25 to 45 gm. of plasma protein would indicate a transfusion not much greater than 500 to 750 cc. These authors did not observe an increased nitrogen excretion in the post-transfusion period. In the present study, approximately twice this amount (*i. e.*, 1000 cc.) of plasma was injected daily for 5 days. Albright² recently reported a nitrogen balance study on a patient who was transfused with 32.1 gm. of nitrogen in the form of serum over a period of 2 days. He concluded that "15.3 gm. were metabolized as indicated by increased nitrogen in the urine and 20.1 converted into protoplasm as indicated by the decreased phosphorus in the urine. . . . The peak of the nitrogen excretion curve came on the day following the 2 days of injection and the increase of nitrogen excretion was completed by the 6th day following the injection." While the total amount of plasma transfused was less than that given to our patients, the amount given per day was larger. The increased nitrogen excretion noted by Albright following the transfusion is in keeping with the findings of the present study. Thus, it seems quite probable that the increased nitrogen excretion in the post-transfusion period was affected by the quantity transfused.

Blood Studies. The alterations in blood and plasma will be considered under plasma volume changes, protein concentration and total circulating protein, and the hematocrit and circulating red cell volume changes.

Reports on changes in plasma volume during and immediately following a transfusion are controversial. Hayward,¹⁵ Hay-

ward and Jordan,¹⁶ and Sharpey-Schafer and Wallace²⁸ have reported a temporary increase in plasma volume in humans which was determined by following hematocrit and hemoglobin changes. The assumption that hematocrit and hemoglobin changes reflect changes in plasma volume has been criticized by Beatti.^{4,5} He points out that a transfusion opens new capillaries and that some plasma can remain immobilized as a surface film without being concerned in the ratio of cells to plasma. Elman and Davey⁹ using the Evans blue dye method found an increase in plasma volume in dogs at the end of a 7 day transfusion period. At the termination of the experimental period (14 to 21 days) the plasma volumes were near the control or below. Shearburn²⁹ noted an immediate but transient increase in total plasma volume returning to the pre-transfusion level within 3 days. An increase in plasma volume following transfusion in dogs has also been noted by Freeman and Wallace¹³ but no greater than was found after injection of glucose or saline. Daft, Robscheit-Robbins and Whipple⁷ noted a decrease in the plasma volume during the period of plasma transfusion, but apparently felt that this was due to a deficient or inadequate protein intake. The subjects in the present study all showed an increase in plasma volume which at the termination of the experiment (9 to 24 days) approached the control value.

There was an interesting inverse relationship between plasma volume and urine excretion. The fluid intake for each individual subject was essentially the same during the control and transfusion periods, except for the additional fluid given in the form of plasma. Subject J. M., who showed an increase of 38% in plasma volume on the 1st day following the last injection, excreted during the period of transfusion an average daily urine volume of only 9% above the control values. Subject C. S., with a 16% increase in plasma volume, excreted a volume of urine 45% above the control value, and the

last subject who showed no significant alteration in plasma volume excreted a volume of urine 132% above the amount excreted previous to transfusion. Metcalf²⁴ in a plasma transfusion study in dogs observed that 4 to 8 hours following an injection, the rate of urine excretion correlated relatively well with the change in plasma volume.

The first subject, J. M., showed little change in protein concentration, but it was significantly increased in the last 2 subjects. The percentage increase in total circulating protein in all 3 subjects was of similar magnitude. However, as shown in Table 4, this rise was small compared to the amount injected. This observation was also noted by Elman.¹⁰ The protein or its metabolites cannot be accounted for in the urine since urinary nitrogen was decreased at the time that the plasma protein was disappearing from the blood stream. Metcalf²⁴ in an attempt to determine if the protein was taken up by the liver, transfused serum directly into the portal vein. However, in this experiment, the protein appeared in the general circulation and then disappeared from the blood stream at about the same rate as in other experiments. No demonstrable change in protein content was noted in liver, muscle, kidney and intestine biopsies before and 8 to 10 hours after a large serum transfusion. The studies of Madden and Whipple²⁵ have indicated a rapid exchange between tissue and plasma protein which has recently been confirmed by studies¹² with the use of labelled plasma protein. But further studies are needed to give information on the storage, excretion, utilization or fate of injected plasma protein.

The change in hematocrit in the first subject was largely due to dilution since it was not accompanied by a decrease in circulating red cell volume. But the hematocrit and circulating red cell volume change in the last 2 subjects was marked. Although the method, which was used to determine the circulating red cell volume is recognized to be inaccurate,¹⁴

the changes noted in these subjects seem marked enough to be of significance. Metcalf²⁴ noted a decrease in size of red cells a few hours following a transfusion in dogs. If this change occurred in these 2 patients, it could only partially account for the marked drop noted in those 2 subjects. Hematologic studies in these 2 patients showed an increase in reticulocyte count. The first patient, J. M., who received plasma from the hospital blood bank did not show the anemia. Since the last 2 subjects received lyophilized plasma, an inherent property of the lyophilized plasma was considered as a possible cause of the anemia. This plasma was preserved with phenyl mercuric borate (1:25,000), and although the amount present is so small as to be non-toxic, its possible effect was investigated by injecting comparable amounts for 5 consecutive days in 2 dogs. Blood studies on these 2 animals were followed for a period of 10 days following the last injection, but at no time was there a demonstrable change in the hematocrit or circulating red cell volume. The possibility that the process of lyophilization may alter the nature of the plasma protein has been previously discussed.

Shearburn,²⁹ in a study on dogs, comments that the total blood volume decreased due to an increasing anemia in 2 groups of animals given a transfusion of 50 cc. of plasma once or twice daily for 2 weeks.

While it is felt that some inherent quality in the lyophilized plasma (possibly a denatured protein) may have caused the anemia, other factors such as repeated large transfusions, cannot be definitely excluded.

Summary. Nitrogen balance, plasma volume, protein and hematocrit determinations were carried out on 3 male subjects given an adequate carbohydrate, mineral and vitamin intake by mouth and protein by plasma transfusion for a period of 5 days. Previous to, and following the transfusion, protein was given

by mouth in the form of a hydrolysate of casein. The results were as follows:

1. During the period of the transfusion, the urinary nitrogen excretion was decreased in all subjects resulting in a marked positive nitrogen balance.

2. Following this period, the urinary nitrogen excretion was increased over the control periods in all 3 subjects resulting in a loss of 13, 87 and 50 % respectively of the nitrogen gained during the period of transfusion. The variation in loss among the 3 subjects may have been due to difference in age, the use of reconstituted lyophilized plasma in the latter 2 subjects, or level of protein intake following the transfusion. Reaction to the plasma transfusion did not seem to have a great effect on the nitrogen balance. There is some indication that the increased

nitrogen excretion during the post-transfusion period may have been due to the quantity of plasma transfused.

3. Nitrogen excretion and partition in 2 of the subjects on a protein-free diet showed some similarity to that noted during the period of transfusion, except for the amount of creatine excreted.

4. The increase in plasma volume was variable in the 3 subjects, but appeared to be inversely related to the volume of urine excreted.

5. The increase in total circulating protein varied from 33 to 52 % but was small compared to the amount of protein injected.

6. Two of the subjects showed an anemia following the plasma transfusions as evidenced by a decrease in calculated circulating red cell volume.

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PARTIAL MATURATION OF LEUKEMIC MYELOBLASTS FOLLOWING FRESH PLASMA TRANSFUSIONS

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In a case of acute myelogenous leukemia, Sabin, Austrian, Cunningham and Doan⁷ found that following whole blood transfusions some of the myeloblasts in the peripheral blood were replaced by early stages of myelocytes. Following each transfusion the percentage of myeloblasts in the differential count declined, while the percentage of early myelocytes rose. After a few days, a relapse occurred and the differential count returned to its original condition, so that these cell types bore an inverse relationship during the period of investigation. It was not known if the factor causing the partial maturation of the myeloblasts was in the transfused cells or in the plasma, nor could the manner of its action be determined. Recently 2 cases of acute myeloblastic leukemia afforded an opportunity to make a further step in investigation. Both patients were in good clinical condition, in spite of the gravity of their disease, and had no need of whole blood transfusions. They were given fresh plasma transfusions to see if the partial maturation described above could be confirmed. The blood plasma was obtained by allowing the cells to settle out of the citrated blood obtained from donors, and was therefore about 2 days old at the time it was given to the patients.

The differential counts were made from dried smears stained with Wright's stain and from supravital preparations. Neutrophil granules when they first appear in the youngest promyelocytes do not stain well with the former method, or for

that matter, with any of the Romanowsky stains. Supravital staining with neutral red and pinacyanole when properly done and when studied with the best available optical system under optimum conditions for microscopy makes possible considerably more accurate differential counts of the earliest cells containing specific granules. This method was therefore used in constructing the curves subsequently referred to in this paper. There is at present, however, some misapprehension about the appearance of myeloblasts and neutrophilic myelocytes A when studied in supravital preparations, because in the early work with the method^{2,7} no distinction was made between neutral red vacuoles and neutrophil granules, which also stain with neutral red. In the above quoted papers, a myeloblast was defined as a cell with a basophilic cytoplasm, having a large number of mitochondria in the cytoplasm and containing no bodies staining with neutral red. Myelocyte A was defined as containing a small number of granules, not more than 10, staining with neutral red, clumped together in the cytoplasm near the centrosphere. These "granules" were thought to be the precursors of the neutrophilic granules, because they stained much more intensely than do the granules of adult neutrophils. The present writer feels that this is a misinterpretation, and that these "granules" were actually neutral red vacuoles. It will be noted in the plates of the first paper cited that the neutral red bodies are drawn as large or larger than the

* This work was done while the author was a member of the Department of Anatomy, Albany Medical College, Union University, Albany, N. Y. He wishes to acknowledge his indebtedness to Dr. Otto A. Faust, Professor of Pediatrics in the Albany Medical College, and to the Resident and Intern Staff of his Department for the courtesy and cooperation which made an exhaustive study of these cases possible.

mitochondria. This is within the size range attained by vacuoles, whereas neutrophilic granules are very much smaller, and are just visible as separate granules when the greatest possible resolving power of the microscope is employed by immersing the condenser. The cells illustrated are therefore not myelocytes A but myeloblasts, for a cell cannot be designated as one of the myelocytes until it has acquired definite specific granules. Hall³ was apparently the first to notice that myeloblasts may contain neutral red vacuoles. All of the myeloblasts of Case 1 of this paper contained neutral red vacuoles, and some of the cells had a large number of them: 70 to 80 per cell, in addition to the usual number of large mitochondria. The myeloblasts of Case 2, however, were apparently somewhat younger and a small number of them never acquired any neutral red vacuoles, even after several hours on the supravital slide. These vacuoles as was noticed by Cunningham, Sabin and Doan² were of a more reddish color than the neutrophil granules of mature cells. However, there is also a slight difference in color between vacuoles and neutrophil granules when the latter first appear around the "centrosphere" (Golgi apparatus), inside of the clump of vacuoles, as described by Simpson and Deming.⁹ This slight difference in color was not noticed by the above-mentioned 3 investigators or by Hall, probably because the optical systems they employed did not have sufficient color correction and resolving power to make the difference visible. This question will be discussed more fully in another publication.

Meanwhile a myeloblast in a supravital preparation will be redefined as an undifferentiated cell normally found in the bone marrow, with a large nucleus having a fine chromatin reticulum and a colorless or faintly yellow cytoplasm which contains large scattered mitochondria and may or may not contain neutral red vacuoles, but in which there are no neutrophilic or other specific granules. Myelocyte A will be redefined as the first cell of the granulocytic line which contains a small clump

of specific (neutrophilic) granules clumped around the "cytocentrum" (Golgi apparatus), the diameter of the whole clump of neutrophilic granules not being greater than 3 times the diameter of the cytocentrum. Most of these cells have an irregular ring of vacuoles around the periphery of the clump of granules, as has already been mentioned, and in addition there may be a variable number of vacuoles scattered in the cytoplasm. Myelocyte B is any cell with more than the above number of specific granules, but less than the full complement, while myelocyte C is a cell with the full complement of granules but with a round or oval nucleus to distinguish it from the later stages of the granulocytic lines. Myelocytes B and C have neutral red vacuoles as well as specific granules in their cytoplasm, but their number decreases as the cell matures.

Case Reports. CASE 1. This patient was a 6 weeks old male infant who had been born with what subsequently proved to be a leukemic tumor of the lower lip. No blood studies were done until the child was referred to the Albany Hospital for diagnosis of the tumor, at which time the leukemia was discovered. The patient was studied for 10 days. The total white blood count during the period of observation varied from 16,000 to 26,000, while the red cell count remained in the vicinity of 3,000,000 cells per c.mm. Blood platelets were reduced, but there was no purpura or other bleeding. The range of cells in differential counts made from smears stained with Wright's stain for the 1st week of hospitalization was as follows: segmented neutrophils 0 to 0.5%, band forms 1 to 2.5%, metamyelocytes 0 to 1.5%, myelocytes 0 to 0.5%, promyelocytes 0 to 2%, leukoblasts and myeloblasts 56 to 61%, monocytes 0 to 0.5%, lymphocytes 36.5 to 41.5%. Congenital leukemia is extremely rare, and this case will therefore be reported in detail elsewhere.

The results of differential counts of myeloblasts and early myelocytes made with the supravital method in this case are shown in Figure 1. It can be seen that for the 1st week, the number of myeloblasts and pro-

myelocytes (myelocytes A and B) was approximately equal, though the percentage varied somewhat from day to day. The uppermost curve on the chart shows the combined percentages of myelocytes A and B, while the lowermost one shows the percentage of myelocytes B, which for this period of time varied from 0.5 to 2.5%. The great majority of these cells had only slightly more neutrophil granules than myelocytes A. The combined curve was drawn because it is a matter of opinion

number of myelocytes A and B increased from 4460 to 10,340 per cc. There can be no doubt therefore that the fresh plasma transfusion produced a partial maturation of some of the myeloblasts. This maturation process is by no means to be interpreted as a clinical remission following the plasma transfusion. When studied on the dried smears stained with Wright's stain, it was much less obvious. The percentage of myeloblasts having an acidophilic spot in the cytoplasm (the clump of discretely visible

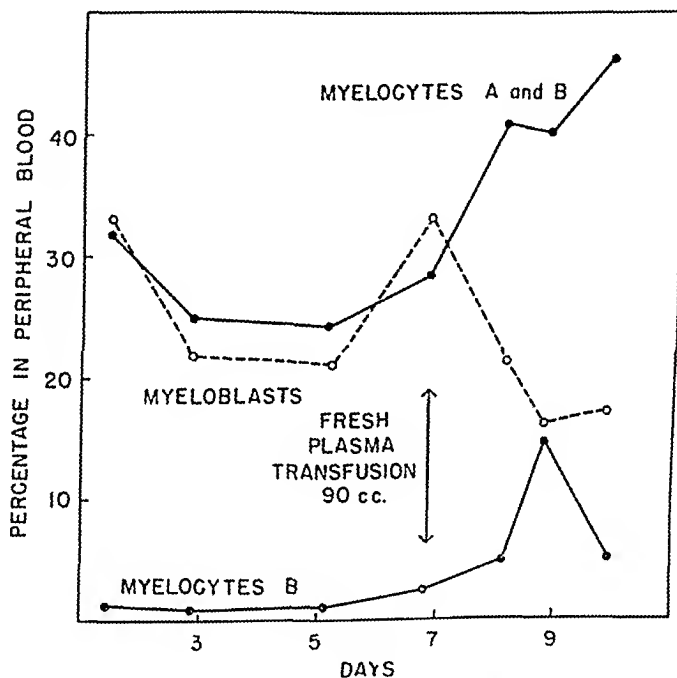


Fig. 1.—Maturation of myeloblasts produced by a fresh plasma transfusion in Case 1.

whether a particular cell is a late myelocyte A or an early myelocyte B. The presence or absence of neutrophilic granules is, however, a more objective criterion and a sharp distinction between myelocyte A and myeloblasts can be made by any competent observer who has an adequate optical system and who uses it with some regard for the principles of good microscopy.

On the 7th day, a 90 cc. transfusion of fresh plasma was given without reaction. On the following 3 days the percentage of myeloblasts significantly decreased (Fig. 1), while the percentage of myelocytes A and B significantly increased. During this period the absolute number of myeloblasts decreased from 5280 per cc. to 3890, while the

neutrophil granules in the supravital preparations) increased somewhat, and those with a uniformly basophilic cytoplasm were somewhat fewer after the transfusion. It is, however, very difficult to decide whether some cells have or do not have a very faintly acidophilic spot, and impossible to place much confidence in observations in which the subjective element is so great. The number of myelocytes A always exceeded the number of myeloblasts having an acidophilic spot in the cytoplasm, showing that neutrophilic granules do not stain in Romanowsky preparations for some time after they can be demonstrated with neutral red in the living cell.

CASE 2. This patient was a well-developed, well-nourished 13 year old white school boy who was admitted to the hospital with complaints of fever, cough, with blood-streaked sputum, swelling of the neck and malaise of 3 days duration. There were areas of petechiæ in the axillæ and groins and scattered petechiæ on the abdomen and chest. Bluish subcutaneous nodules about 0.5 cm. in diameter were scattered over the cheeks, neck, arms and thighs. The gums were hypertrophied, tender, ulcerated and bled easily. The pharynx was injected, the tonsils large and the left one covered with a necrotic yellowish membrane. There was generalized lymphadenopathy, and the spleen was palpable 3 cm. below the costal margin. The liver was not palpable. The blood count on admission showed 13 gm. (88%) hemoglobin, 4,350,000 red blood cells and 34,400 white blood cells per c.mm. The differential count on admission was segmented neutrophils 6%, lymphocytes 5% and large, primitive looking cells having nucleoli 89%. The latter cells were subsequently identified as myeloblasts. The patient was studied for 3 weeks. During the period of hospitalization the hemoglobin varied from 10 to 13.5 gm., and the red blood count from 3,480,000 to 4,600,000. The white cell count after admission rose to 75,900 in the 1st week, declined to 28,100 at the end of the 2nd week, and then rose again to 48,000 on the day of final discharge. The range of the neutrophilic cells in the differential counts was as follows: segmented neutrophils 1 to 6%, band forms 0.5 to 3.5%, metamyelocytes 0 to 2%, myelocytes 0 to 0.5%, promyelocytes 0 to 2.5%, and (with Wright's stain) myeloblasts 77.5 to 89%. The lymphocytes varied from 5 to 16.5%, and occasional eosinophils and basophils were found. No monocytes were seen in this case either with Wright's stain or with the supravital method.

In Case 1, the myeloblasts when stained with Wright's stain all contained considerable numbers of azure granules, and when studied in the supravital preparations, the number of myeloblasts and myelocytes A were approximately equal as has been described. In this case, however, the cells were much more primitive, and when stained with Wright's stain during the 1st week the patient was under observation, only 8.5 to 15.5% of myeloblasts contained azure

granules, and at no time did more than 26.5% of them show azure granulation. When studied with the supravital method during this time 70 to 80.6% of the cells in the differential count were myeloblasts and only 5 to 12.5% were myelocytes A (Fig. 2). No myelocytes B were seen during this period, and only a small number of them subsequently. They have therefore been left off of the chart. Peroxidase positive cells made up 5 to 8.5% of the differential count.

On the 8th hospital day, the patient was given a 400 cc. transfusion of fresh plasma, without reaction. Following this the number of myelocytes A rose to 20.5%, but within 3 days after the transfusion declined again to 12%. A second fresh plasma transfusion was then given, followed by a rise of myelocytes A to 26% in 24 hours, and then a decline to 10.5% in the 3 days following the transfusion (Fig. 2).

The patient was then taken home by his family, but returned to the hospital 3 days later, somewhat dehydrated, complaining of pain from his cough and difficulty in swallowing which made feeding him at home impossible. After these complaints had been relieved as much as possible by suitable medication, the patient was given 2 intramuscular injections of 17% gamma globulin solution to see if the substance which produced the partial maturation of the myeloblasts is present in that plasma fraction. The first injection was made with 10 cc. into either buttock, the second with 15 cc. into either buttock 24 hours later. Each intramuscular injection was preceded by 2 cc. of 0.5% novocain through the same needle, and produced a minimum amount of discomfort to the patient. This amount of gamma globulin was given upon the assumption that 25 cc. of this solution would contain about the same amount of gamma globulin as a 500 cc. fresh plasma transfusion. These injections were, however, without effect on the differential count (Fig. 3). The following day the patient was given a 250 cc. transfusion of commercial dried plasma ("Lyovac"), made up so as to contain as much protein as 500 cc. of fresh plasma. This also had no effect on the differential count (Fig. 3).

On the 5th day after his second admission the patient was again taken home by his

family, and died a few days later. No autopsy was obtained.

COMMENT. Leukemic cells have been grown in tissue culture with a variety of media and methods.^{1,5,6} All authors who have studied the problem agree that there are no marked differences in behavior be-

tween leukemic cells and normal cells, and that the younger cells in the cultures mature to older forms. It is reported that myeloblasts will develop granules and eventually transform into adult granulocytes. In acute myeloblastic leukemia, relatively few of them seem to be able to accomplish

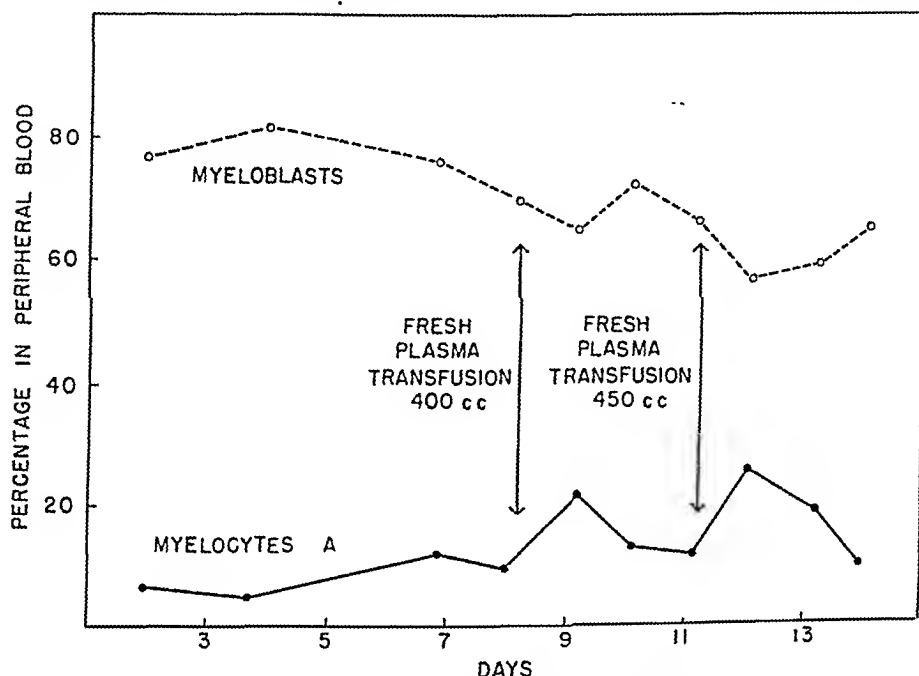


FIG. 2.—Maturation of myeloblasts produced by fresh plasma transfusions in Case 2.

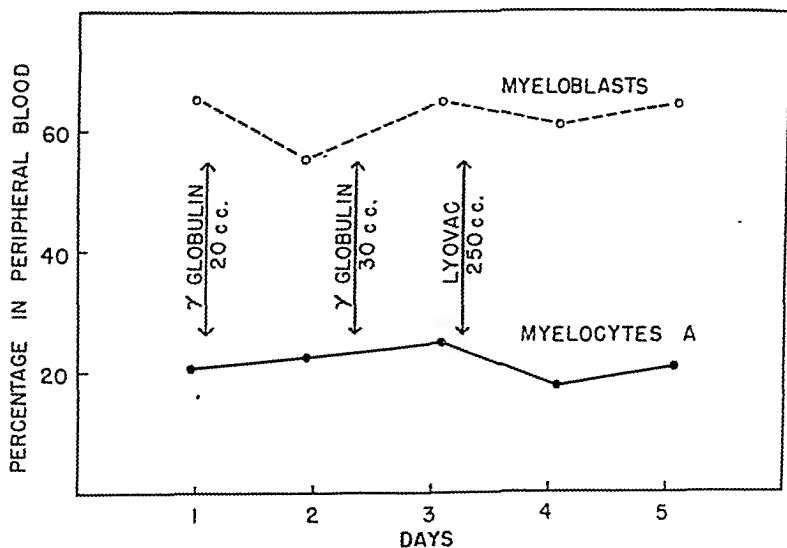


FIG. 3.—Absence of maturing effect following administration of gamma globulin and Lyovac plasma.

this change in the body of the patient. It is possible that an inhibitor substance is present, which prevents the maturation of the myeloblasts. It would seem more likely, however, that there is some substance missing from the environment of such cells while they are in the body, the lack of which prevents their maturation. Evidence of this was obtained by Timofejewsky and Benewolenskaja,¹⁰ and more recently by Houghton⁴ in experiments in which myeloblasts of acute myeloblastic leukemia were grown in tissue cultures with normal plasma as the medium. After a time, the cultured myeloblasts began to mature. This significant finding is confirmed by the present experiments, which show that fresh normal blood plasma will produce a maturing effect on the myeloblasts of acute myeloblastic leukemia *in vivo*, just as it does in tissue culture. The maturation produced in the patient is, however, only partial and is moreover of a transitory nature, possibly because the substance producing it is present in very small amounts in the plasma and is quickly used up. There is a limit to the amount of plasma which can be given to a patient without getting into serious difficulty with the fluid balance. In tissue cultures, the appearance of specific granules in the cultured myeloblasts takes place in a matter of hours. It is realized that much more frequent differential counting of these cases would have been desirable, but the exigencies of a war-time teaching schedule made this impossible. A preliminary note on this work has been published.⁸

The essential results of Sabin, Austrian, Cunningham and Doan, namely that whole blood transfusions cause maturation of the myeloblasts of acute myelogenous leukemia, are confirmed by the present work, even though, as has been shown, it is impossible to be sure which cells they were counting as the more mature forms. It has been further shown that the maturing substance is carried in the plasma, and is not some factor liberated by the breakdown of transfused blood cells.

The substance which causes the maturation of the myeloblasts is not present in the gamma globulin fraction of the plasma, at least in the form in which this fraction is currently available. It is not present in ordinary dried plasma, if 1 test is a reliable criterion. Possibly it is destroyed during the processing and subsequent dehydration. It need hardly be added that the nature and amount of this substance present in fresh plasma are completely unknown.

Summary. 1. Fresh plasma transfusions resulted in the partial maturation of myeloblasts in 2 cases of acute myeloblastic leukemia.

2. The results of other authors with whole blood transfusions are thus confirmed.

3. Fresh plasma will cause the partial maturation of leukemic myeloblasts *in vivo* as well as *in vitro*.

4. The substance causing the maturation is not present in the gamma globulin fraction of blood plasma or in dried plasma.

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GYNECOMASTIA ASSOCIATED WITH VITAMIN DEFICIENCY DISEASE

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AN outbreak of gynecomastia was observed among the Americans held as Japanese prisoners-of-war in the Philippine Islands. This group of 7000 to 8000 surrendered on Bataan April 9, 1942, and was liberated Jan. 30, 1945. During these 34 months malaria, dysentery and vitamin deficiency disease attacked almost every man in camp.² The prisoners were always underfed, suffered from all the avitaminotic states, acute and chronic bacillary and amebic dysentery, and malaria.

The appearance of enlarged breasts did not closely coincide with the onset of any deficiency disease. Nutritional edema, pellagra, ariboflavinosis, beriberi, peripheral neuritis, scurvy, xerophthalmia and corneal ulceration had their onset in approximately that order between April and December 1942. The first cases of gynecomastia were seen in November 1943, or after $1\frac{1}{2}$ years of prison life, almost 1 year since the appearance of a new deficiency disease. During this period there was a relative increase in diet providing approximately 1200 to 1400 Calories and a corresponding decrease in the incidence of malaria and dysentery.

The census of the camp at this time was about 5000, of which 500 (10%) had breast disturbances. They were of military age, almost all between 20 and 30 years. This group did not necessarily represent the severest cases of malnutrition, although there was usually a history of many deficiency diseases. Almost all of the men had gained from 10 to 50 pounds in the few months just prior to the "epidemic" of gynecomastia. There was no particular type of habitus among the involved men.

The onset of gynecomastia was insidious

but simultaneous in this group. It is impossible to say how long the process had been active, but within 2 to 3 weeks a small tumor appeared. Both breasts were involved, usually to the same degree, and the size was comparable to the breast of an adolescent girl. An irregular, firm, nodular mass, attached to the nipple but freely movable over the deep structures, could be felt. This was usually not tender except after trauma. Thin, slightly milky fluid was expressed in a few cases, but this was not the rule. The maximum size of 2.5 to 3.5 cm. in diameter was reached in 2 to 3 months, and regression was complete in about another 3 months.

A few men continued to have nodular breasts, although small, even until liberation 1 year later. There were no changes in hair distribution or pitch of voice. The size of testicles almost always remained unchanged, although 5 or 6 men had lost a testicle during the period of vitamin A deficiency, due to suppurative orchitis. Symmetrical enlargement of one or both testes was observed in rare cases. Potency and sexual desire and nocturnal emissions were not noticeably changed, having been at a very low level before gynecomastia appeared. Sperm counts were not obtainable. The rest of the examination revealed severe malnutrition, residual signs of neuritis and pellagra.

Weekly examinations were done on a group of 100 men with gynecomastia. The course was one of steady progression and then regression, completed within 6 months after onset. We became satisfied that the lesion was self-limited, and no treatment was suggested. Improvement coincided with a shipment of Red Cross food and sufficient vitamins to pro-

vide each man with 1 vitamin capsule* daily beginning in January 1944. A small number of men continued to show a progressive enlargement of the breast after 6 months. These breasts were surgically removed. Macroscopically there appeared to be small projections of tissue in the ducts, intracanalicular fibro-adenomas. No facilities were available for microscopic examination.

Discussion. A causal relationship was never definitely established, but the most obvious explanation was a disturbance due to vitamin deficiency. We thought that the severe prolonged malnutrition had temporarily upset the endocrine balance. There was no clinical evidence of degeneration of the liver which might have resulted in an excess of estrogen in the systemic circulation.¹

It is interesting to note that shortly

after the disappearance of the gynecomastia we discovered blood pressure readings above 140 mm. systolic and 90 mm. diastolic in about 60 % of the entire personnel. No attempt was made to check the blood pressure of those patients who had recovered from gynecomastia. The hypertension was transitory, lasting from 4 to 6 months, and adrenal dysfunction was the suspected cause.

Conclusions. 1. About 500 cases of gynecomastia were seen in males after severe, prolonged malnutrition. It appeared many months after the onset of any of several deficiency diseases, while there was a relative increase in diet.

2. There appears to be a relationship between endocrine balance and adequate vitamin intake.

3. Transitory hypertension may be further evidence of this relationship.

* These capsules were vita-kaps, each containing Vitamin A, 5000 U.S.P. units; Vitamin D, 500 U.S.P. units; Vitamin B₁ (thiamine), 333 U.S.P. units (1 mg.); Vitamin C, 600 U.S.P. units (30 mg.); Vitamin G (riboflavin) 2 mg.

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THE EFFECT OF PATENT DUCTUS ARTERIOSUS ON BODY GROWTH*

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REVIEW of key publications^{1,3,4,5,6} dealing with various aspects of persistent patency of ductus arteriosus reveals no essential concern with the effect of this congenital vascular lesion on body growth.

Evaluation of the effect of any one factor on body growth is difficult because of the complexity of growth influences in general, but the problem is to a degree simplified by the nature of the physiologic disturbances concerned in patency of a ductus arteriosus. Most if not all elements influencing growth are transported to the tissues of the body through the blood stream. It is reasonable to infer that a lessening of the quantity of blood reaching the tissues, or a reduced concentration in the blood of growth promoting elements, will influence the rate of body growth. And if one or both influences persist through the growth period, stunting will result.

The degree of patency and the consequent dynamic alteration of the circulation varies greatly in magnitude. The shunt of blood from the aorta to the pulmonary artery may vary from a few cc. to 70%² or more of the output of the left ventricle. Manifestly in many patients the normal quantity of blood delivered to the left ventricle by the right ventricle is shunted from the aorta so that physiologically sufficient quantities do not perfuse the body tissues; the deficit depending upon the size of the patency and the capacity of compensating mechanisms.

One is rarely impressed with the smallness (height and weight) of many patients who have patent ductus arteriosus until he observes them in very striking contrast of body size with their parents, brothers, sisters, and children.

This study is concerned with 3 patients.

The charts are designed to show the contrasting physical size, height, weight, and body surface area in square meters. No factor other than the patent ductus could be found to account for the smallness of each of the 3 patients, and when the ductus was successfully closed in one, he outstripped his twin in height in less than 3 years.

Case 1. (Fig. 1) a female, aged 23, had a ductus 1 cm. in diameter at operative ligation. This patient had gross cardiac enlargement and early congestive failure. She was considerably shorter and less heavy than her parents, brother, and sisters.

Case 2. (Fig. 2) a mother, aged 34, is considerably shorter and less heavy than her parents, brothers, sisters, and her own child, aged 15.

Case 3. (Fig. 3) one of identical male twins, aged 11, the other normal. The one with a gross patency was both shorter and lighter than his twin; 35 months after surgical cure, he had grown 16.4 cm. which was 6.1 cm. more than the growth of the normal twin.

Discussion. At the beginning it was admitted that the evaluation of growth inhibiting factors is difficult, yet a study of the charts is convincing that a factor did exist in these patients which inhibited the anticipated genetic growth influences.

All 3 of the patients enjoyed good home environments, had no peculiar food habits, and economically were in the upper strata of society.

They had each been peculiarly free from infections and from a physical standpoint were normal except for body size and the cardiovascular defect.

None of the patients were interested in sports requiring physical activity. They

* Presented at the 59th Meeting of the Association of American Physicians, May 1946.

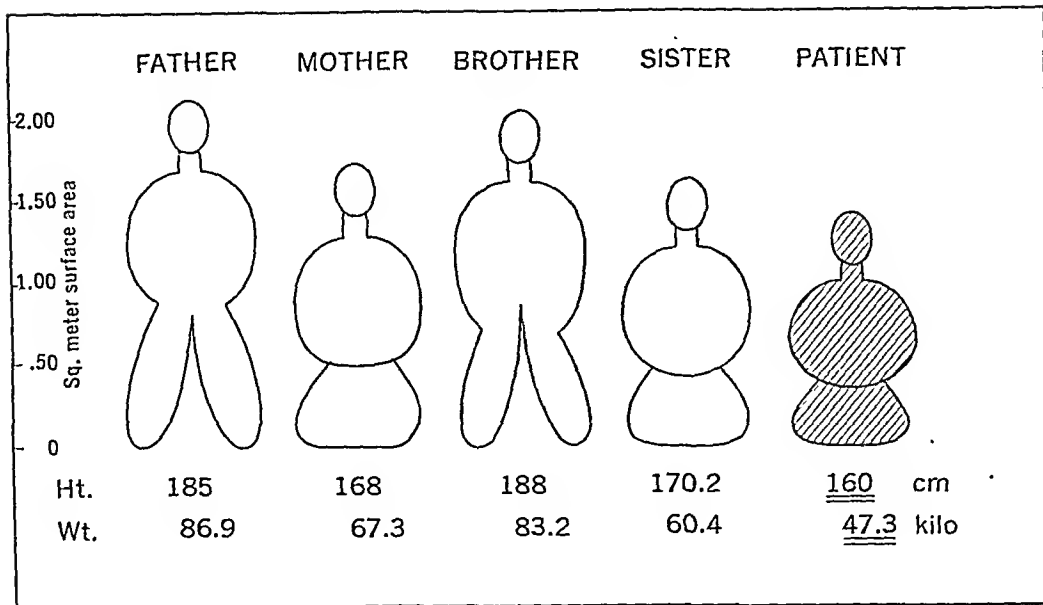


FIG. 1.

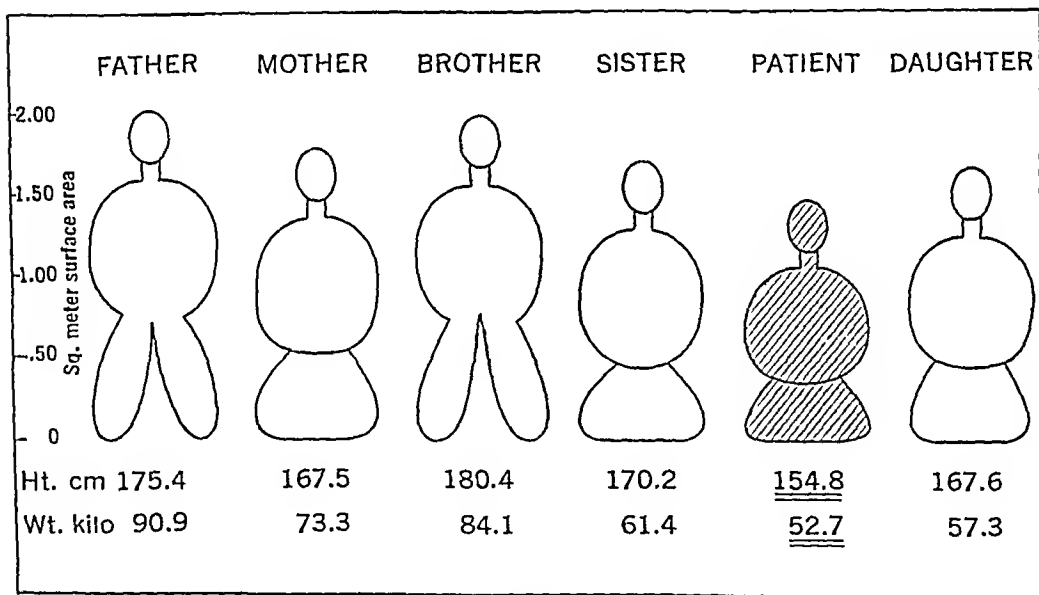


FIG. 2.

	PATIENT		BROTHER	
May 1943	Ht. cm	Wt. kilo	Ht. cm	Wt. kilo
	146.1	32.2	149.8	35.9
	Operation			
April 1946	<u>162.5</u>	40.9	160.1	45.5
	Growth in 3 years 16.4 cm		Growth in 3 years 10.3 cm	

FIG. 3.

stated that they simply did not enjoy such exertion; however it is more likely that they had been inhibited by physical limitations. Non-participation in sports is not a logical explanation for the stunting of growth.

In this connection it is interesting to comment on the twins. Before operation the twin with the patent ductus took little exercise. Since his recovery he has become even more active physically than his normal twin brother. This may be an explanation for the fact that his weight has not kept pace with the growth in height. Skeletal growth, after all, is much more significant in a youth of the patient's age than the accumulation of fatty tissue.

Finally it must be emphasized that if a patent ductus arteriosus retards body growth its effects will be clinically impressive only in those patients in whom the circulatory shunt is of considerable magnitude. Even in these patients compensatory adjustments may in some instance

so nullify the effects that growth is normal. It is doubtful therefore, if there is an absolute ratio existing between the size of the patent ductus and the consequent growth inhibition for the complexities of biological results cannot be predicted by mathematical equations.

Summary. The charts show these patients to have been definitely influenced by some factor resulting in positive inhibition of body growth. The only apparent and consistent influence is that of patent ductus arteriosus, presumably due to the lessening of the normal supply of blood to the body tissues.

The rapid increase in height observed in the twin after operative closure of a patent ductus is impressive and convincing.

In many patients the growth inhibiting factor is an added reason for surgical ligation of a patent ductus arteriosus.

The optimum period for operation is probably before the age of 11 years.

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HEBERDEN'S NODES

VI. THE EFFECT OF NERVE INJURY UPON THE FORMATION OF DEGENERATIVE JOINT DISEASE OF THE FINGERS

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AND

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HEBERDEN'S nodes are enlargements of the terminal interphalangeal joints of the fingers due to degenerative joint disease. Although the process always starts in one finger it soon spreads to others until several fingers of both hands are affected. It is the purpose of this presentation to describe a series of cases in which Heberden's nodes failed to appear in one hand which was the site of serious trophic nerve disorder although deformities had developed to a severe degree on the healthy or non-paralyzed side.

Isolated nodes occurring in a single finger, the result of direct injury and most often seen in males, do not spread to uninjured digits and are not to be confused with the so-called idiopathic Heberden's nodes with which the present discussion is particularly concerned. Former studies indicate that the formation of idiopathic Heberden's nodes is influenced by sex, age and race, being most common in white women after the age of the menopause.⁸ The most important factor so far recognized in etiology is heredity.^{9,10} The hereditary influence was indicated by observing that the mothers of affected women were involved twice and the sisters 3 times as often as women in the general population. The distribution of involvement among family pedigrees together with gene frequency analysis supported the hypothesis that the genetic mechanism of idiopathic Heberden's nodes involves a single autosomal gene, sex influenced, dominant in females and recessive in males.

Although susceptibility to this condi-

tion depends upon genetic and constitutional factors, clinical evidence indicates that Heberden's nodes develop only in a hand which has an intact nerve supply, which functions normally and in which the tissues are not subject to trophic disorder. The lesion fails to develop or is retarded in its progress in the presence of either peripheral nerve damage, spinal cord disease or palsies of cerebral origin. This fact is demonstrated by 3 cases we have observed and are describing herewith and by 9 cases described in the literature and by personal communications. The first case is one of a woman with a peripheral nerve lesion.

Case Abstracts. CASE 1. Mrs. E. V., a 53 year old white woman, was first observed in 1939 because of enlargements of the finger joints. There was no history of joint disease in the parents. The patient was the fourth of 8 children, 5 of whom are living. The oldest sister, age 61, reported by correspondence that her right forefinger became enlarged 4 years before and that the joints of all the fingers of the right hand and the forefinger of the left hand are now enlarged. Another sister, age 56, reported by correspondence an enlargement of several fingers of 2 years duration.

Past History. There were no serious illnesses or major operations. At the age of 41, 12 years ago, the patient sustained a deep laceration from a broken milk bottle in the left palm through the thenar eminence resulting in a paralysis of the index and middle fingers and a partial paralysis of the thumb, ring and little fingers. The menses stopped at the age of 50 years.

since which time she has had frequent hot flashes.

Present Illness. In the right or uninjured hand the forefinger began to enlarge at the age of 50, 3 years ago, since which time all the other fingers of the same hand became similarly involved. The enlargement of the joints which were originally involved continues to increase but at no time has there been any pain or serious discomfort. In contrast only the little finger of the lacerated hand developed joint enlargement, the other fingers having escaped this involvement. Disease of other joints, particularly of the large articulations, has not been demonstrated.

was obviously an injury to the median nerve, shows striking differences from the above. Instead of the typical bulbous appearance of Heberden's nodes, the index and middle fingers of this hand are thinner, have a tapering appearance and seem to be actually longer than their mates. The skin is thin, glossy and relatively free of wrinkles. The index finger shows a flexion deformity of the proximal finger joint, while the middle finger is stiffened and straight. The flexion deformity of the terminal joint of the ring finger can be corrected by passive motion.

A neurologic study of this injured hand indicates that the laceration resulted in a



FIG. 1 —Mrs. E. V. Right hand shows enlargement of the terminal joints of the index and little fingers. In the left hand, the index and middle fingers are thin and tapering. Skin on these fingers is thin, glossy and free of wrinkles. The index finger shows a flexion deformity of the proximal joint while the middle finger is stiffened and straight. The median nerve of the left hand was injured by a laceration 12 years before.

Physical Examination. In the right hand where no nerve injury occurred, the terminal joints of the fingers are enlarged (Fig. 1). This is particularly prominent in the index and little fingers both of which are further deformed by deviation. The normal wrinkling of the skin is clearly marked, especially over the proximal interphalangeal joints. There is no sign of motor weakness and the patient can make a tight fist with a normal closure.

In contrast, the left hand in which there

section of the distal sensory and motor branches of the median nerve. There is marked atrophy of the thenar muscles. The thumb fails to oppose or flex fully in the closure of the fist. Complete active flexion of the index and middle fingers is impossible because of paralysis of the first and second lumbricals. Anesthesia or hypoaesthesia is present along the entire palmar surface of the middle finger and over the distal one-third of the index finger.

Roentgen Ray Studies. In the right or uninjured hand there is a marked lateral enlargement of the proximal end of each distal phalanx with apparent shortening of this bone (Fig. 2). The distal end of each second phalanx shows a bulbous enlargement involving the terminal third of its length most marked in the index finger. Joint surfaces are not distorted. There is a very small spur on the ulnar side of the proximal end of the fifth terminal phalanx. Other joints of the right hand are apparently normal.

evident in the ring and little fingers whose nerve supply is predominantly from the ulnar trunk.

Case Summary. A patient, 53 years old, who had a hereditary predisposition to Heberden's nodes, suffered a median nerve injury of the left hand 6 years before the actual appearance of such nodes. In the area ordinarily supplied by the injured median nerve the skin suffered trophic changes and Heberden's nodes failed to

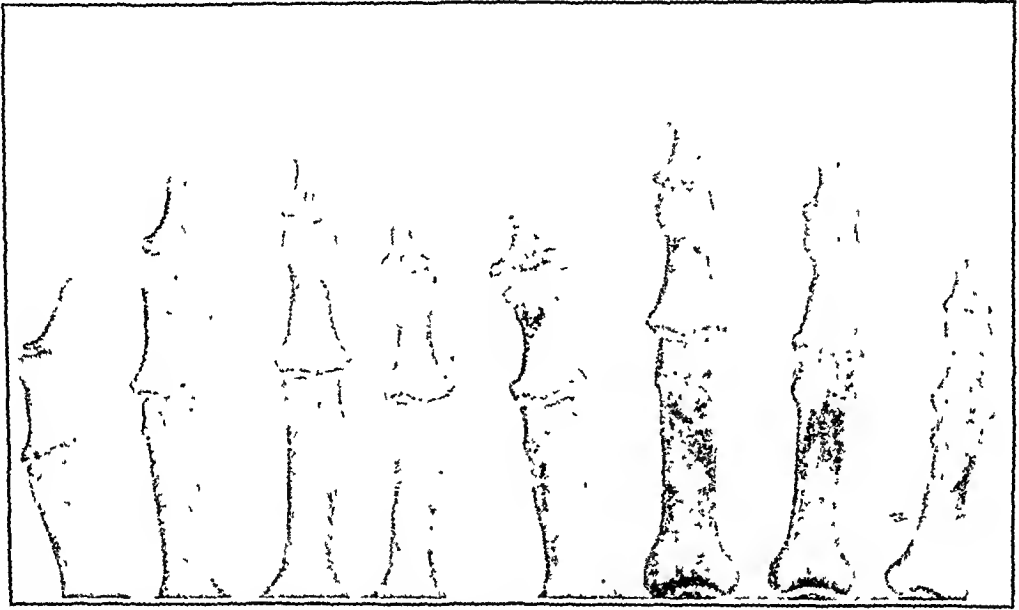


FIG. 2.—Mrs. E. V. Roentgenogram of the fingers of the right hand show marked lateral enlargement of the proximal end of each distal phalanx with apparent shortening of this bone. The distal end of the second phalanx shows a bulbous enlargement involving the terminal third of its length most marked in the index finger. Joint surfaces are not distorted. There is a very small spur on the ulnar side of the proximal end of the fifth terminal phalanx.

Roentgenogram of the left or injured hand reveal marked demineralization of the index and middle fingers being most prominent in the middle and terminal phalanges of these two fingers where the overlying tissues are supplied exclusively by the sensory branches of the median nerve. Flexion deformity, a non-compact bone structure and bulbous enlargement of the terminal joints, signs of mild Heberden's nodes, are evident in the ring and little fingers whose nerve supply is predominantly from the ulnar nerve.

Roentgen ray studies of the left or injured hand reveal a marked demineralization of the index and middle fingers. This demineralization is sharply limited, being most prominent in the middle and terminal phalanges of these two fingers, where the overlying tissues are supplied exclusively by the sensory branches of the defective median nerve. Flexion deformity, a non-compact bone structure and a bulbous enlargement of the terminal finger joints, the signs of mild Heberden's nodes, are clearly

develop in those bones which derived sensory nerve filaments from the injured nerve alone. Nodes did, however, appear in the index and little finger of the uninjured hand and were apparent in the ring and fifth finger of the lacerated hand. Demineralization and failure of node formation was not so pronounced in phalanges which have a double nerve supply, *i. e.*, where the radial or ulnar nerves overlap the median nerve distribution. This sug-

gests that trophic bone disease depends largely upon damage to the sensory nerve supply to the joints and to the periosteum as well as to modification of blood supply.

McEwen⁷ mentioned 3 patients with unilateral Heberden's nodes. In the hand where they did not occur there had been peripheral nerve injuries with obvious trophic changes in the skin. In 1 of these patients, 3 fingers were useful and 2 were paralyzed in the injured hand. There were marked Heberden's nodes on the intact hand, moderate formations on the functioning fingers of the injured hand but no sign of nodes on the paralyzed fingers.

The second case is one of a woman with a lesion of the spinal cord.

CASE 2. Mrs. L. M., a 68 year old white woman was first seen in 1939 because of pain in the right shoulder. Family history revealed no record of joint disease except in the patient's eldest daughter, age 44, who was found on examination to have well-marked enlargements of the terminal joints of all the fingers except the thumbs diagnosed as idiopathic Heberden's nodes.

The *past history* revealed infantile paralysis in early childhood which affected the right arm leaving it smaller and weaker than the left but with no definite paralysis of any one muscle group.

Present illness began 6 years before at the age of 62 with enlargement of the terminal phalanx of the left forefinger. The left little finger became involved only within the last year. Neither of these deformities could be attributed to local trauma.

Shortly after these enlargements were first noted on the left hand, at age 65, the patient sustained a trivial injury to the right elbow, which was followed shortly by pain and stiffness of the right shoulder. The shoulder was later found to be ankylosed and consequently was manipulated under anesthesia. This procedure was followed by immobilization in abduction for several days. Two months later when she was examined, the right arm and hand were painful and useless. The pain and swelling were so severe that an erroneous diagnosis of gonorrheal arthritis had been made. The hand was swollen, the skin was shiny, cyan-

otic, cold and mottled in appearance. The wrist was fixed in partial flexion, the fingers were extended and passive motion was greatly restricted and painful. The sensory findings consisted of an hyposthesia in the fields of the median and ulnar nerves. The motor and sensory defects suggested a mild combined palsy of the median and ulnar nerves.

Roentgenograms taken at the time of her first visit showed marked demineralization and other features typical of Sudeck's bone atrophy in the injured hand and arm. Definite deformity of the left forefinger due to early Heberden's nodes was seen at this time. The median and ulnar nerve paralysis was vigorously treated with heat, massage, active and passive exercise, so that both right arm and hand have regained their former degree of limited function.

Photograph of the hands taken 27 months after her first visit shows the right or atrophied hand to be the same length but definitely more slender than the left. The skin of the partially paralyzed hand is thinner, tighter and shows a marked loss of wrinkling as compared to the left. The terminal interphalangeal joints of the once paralyzed hand are quite small, giving the fingers an appearance of constriction. In contrast the forefinger of the left or normally developed hand shows enlargement, flexion and ulnar deviation of the terminal joint and normal skin wrinkling. The middle finger, as well as the little finger, presents the same bulbous deformities and only the ring finger of the uninjured left hand appears to have escaped the joint deformities characteristic of Heberden's nodes.

Reexamination 6 years later, at age 73, shows the right or partially paralyzed hand to be essentially unchanged in appearance or function. The left or arthritic hand (Fig. 3) shows increased enlargement of all the terminal joints. There are enlargements and lateral deviation of the index, middle and little fingers and enlargement of the ring finger.

Roentgen ray studies of both hands taken at the time of the first visit, 27 months later and finally in 1946, 9 years after the first visit all show marked generalized demineralization throughout the entire bony structure of the palsied hand. The joint surfaces are everywhere smooth and regular

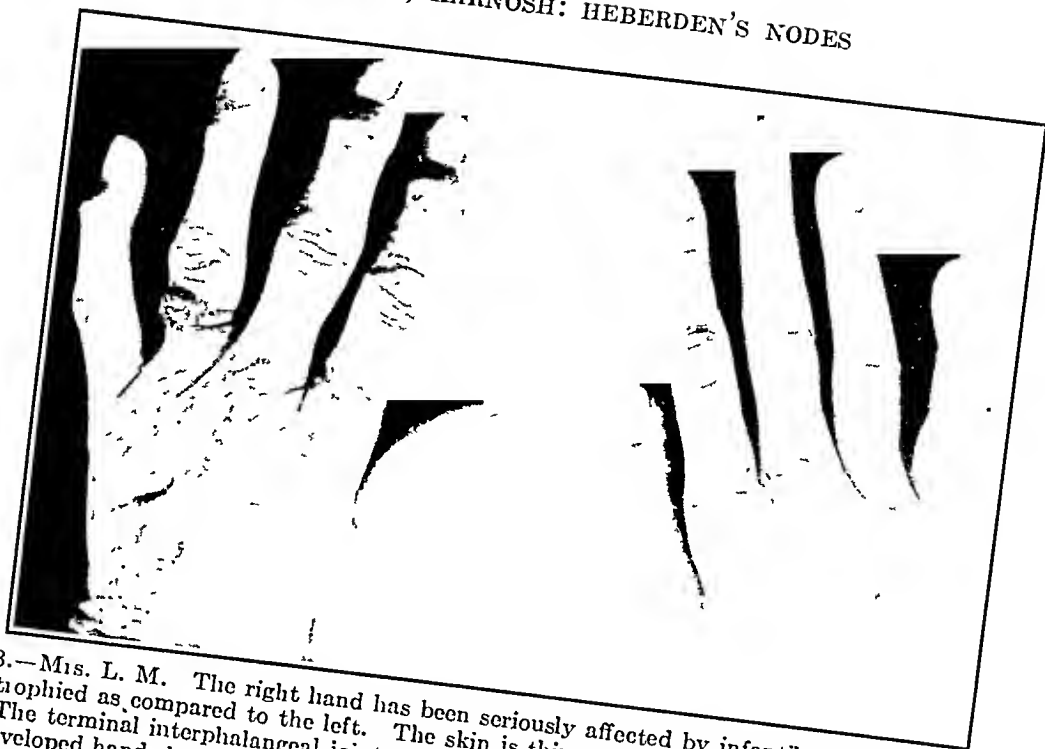


FIG. 3.—Mrs. L. M. The right hand has been seriously affected by infantile paralysis, being definitely atrophied as compared to the left. The skin is thinner, tighter and smoother than on the left hand. The terminal interphalangeal joints are small and appear to be constricted. The left or normally developed hand shows enlargement and flexion deformity of all the terminal joints. The index, middle and little fingers show lateral deviation also.



FIG. 4.—Mrs. L. M. Roentgenogram of the right or palsied hand shows marked generalized demineralization of all bones and extreme thinning of the cortex. The shape of the bones and the contour of the joints are absolutely normal. Roentgenogram of the left hand shows deformity of all the terminal interphalangeal joints. There is decrease of joint space, irregularity of joint line, broadening with spur formation of the proximal end of the distal phalanges and bulbous enlargement of the distal portion of the second phalanges. The other joints of this hand are normal.

and the joint spaces are of normal width. Little or no change is seen in this hand during the period of observation.

Roentgenograms of the left, the unparalyzed or arthritic hand at the time of the first visit, showed arthritic deformity in the terminal joints of the index and little finger. The other fingers were apparently not affected. At the time of the last visit, 6 years later (Fig. 4), the terminal joints of all four fingers show decrease or obliteration of joint space, marked irregularity of joint line, broadening with spur formation of the proximal end of the terminal phalanges and bulbous enlargement of the distal portion of the second phalanges. The other joints of this arthritic hand are normal.

and swelling with Sudek's bone atrophy of the entire right arm. Even at that time, however, definite joint deformity of the left forefinger of the other hand was apparent by Roentgen ray. The pre-existing infantile paralysis with consequence trophic bone disturbance undoubtedly prevented the formation of Heberden's nodes. Nine years after her peripheral nerve injury there was still no evidence of Heberden's nodes on the right hand. Heberden's nodes on the left hand became larger during this period of observation.

Hench⁵ described an elderly woman

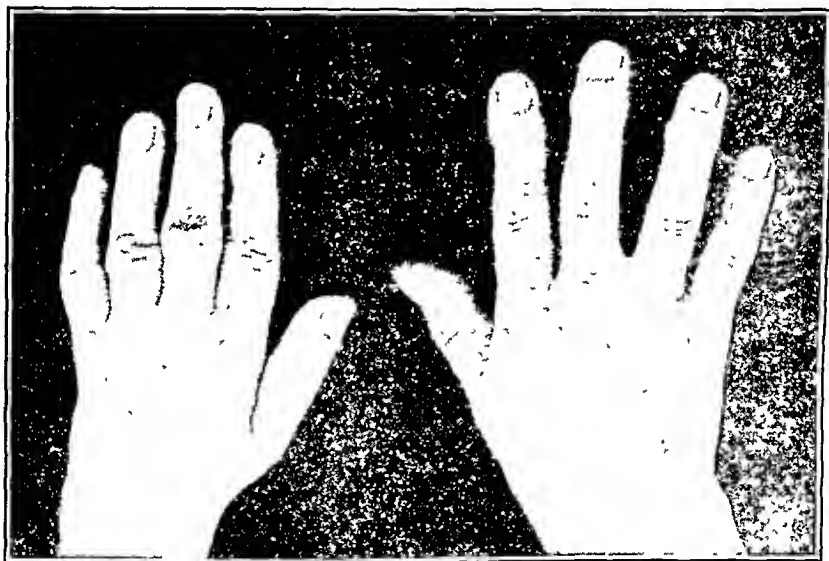


FIG. 5.—Marked Heberden's nodes on the fingers of the right hand only. The left hand has been spared. Patient had infantile paralysis in childhood resulting in partial paralysis and lack of development of the left hand. Photograph and case history by courtesy of Philip S. Hench, M.D., and the Mayo Clinic.

Case Summary. This is a woman 68 years of age when first seen whose right hand was imperfectly developed because of infantile paralysis in early childhood. She had Heberden's nodes of the otherwise normal left hand whose joint disease first appeared 6 years before. At the time of her first visit she had a painful right shoulder which had been manipulated and after which she suffered a mild but definite combined paresis of the right median and ulnar nerves, painful stiffness

who had infantile paralysis as a child with resultant partial paralysis of 1 arm and hand. Despite persistent atrophy and arrested development of this hand, she had slowly regained considerable use of it, so that functional recovery was approximately 50%. Years later definite Heberden's nodes developed on the fingers of her normal hand but no evidence of them appeared on the partially paralyzed extremity (Fig. 5). Beard¹ reports having seen an elderly woman who

suffered infantile paralysis as a child which left her with impaired development and function of the left arm. She had marked Heberden's nodes of all fingers of the right hand when first seen 10 years before her death. There were no Heberden's nodes of the fingers of the left hand.

It has been observed that hemiplegia due to cerebral apoplexy may prevent the development of Heberden's nodes, though they become well marked on the normal side. Forestier³ described a 55 year old woman with a right hemiplegia of 7 years duration who developed Heberden's nodes on all the fingers of the non-paralyzed hand about 8 months after her stroke. His communication included excellent photographs and Roentgenograms of both hands.

The same author presented a second woman who suffered a right hemiplegia due to hypertension at 59 years of age. For 2 years before the attack of apoplexy she observed nodosities on both thumbs and left forefinger. Since the hemiplegia, the degree of arthritis of the right thumb has remained stationary and there has been no extension to the other fingers of the paralyzed hand. However, in the left hand the arthritis has extended to the distal joints of the middle and ring fingers and the proximal joints of the second, third and fourth fingers.

Coste and Forestier² described a 66 year old woman who had a right-sided hemiplegia with facial paralysis and aphasia 9 years before. She had had pain and deformity of the right thumb 10 years before the stroke. One year after the stroke of paralysis, the pain, swelling and stiffness attacked all the joints of the non-paralyzed hand. The process had progressed until she presented a complete but unilateral picture of advanced Heberden's nodes. The right or paralyzed hand remained free of joint disease.

The same authors report a man with hemiplegia of 10 years duration who developed typical advanced Heberden's nodes on the sound side but little or no

evidence of joint disease in the hand on the paralyzed side.

It is seen that Heberden's nodes have failed to develop in the presence of lesions of the peripheral nerves, spinal cord or upper motor neuron lesion. The question arises as to the effect such lesions might have on Heberden's nodes already present. One such case has been observed.

CASE 3. Mrs. C. C. was first seen at the age of 50 with well-developed Heberden's nodes on all fingers of both hands. The enlargements increased in size considerably over a period of 2 years. She suffered a cerebral accident which left her with partial paralysis of her left side. Photographs and Roentgenograms of both hands were made at the ages of 52 and 53, 15 months after her apoplexy. Before the stroke both hands were quite similar. Photograph of the left hand at age of 52 showed marked enlargement of all the terminal interphalangeal joints with flexion deformity and deviation of the index and little finger. Photographs of the same hand after the stroke shows that the enlargement of the joints have become much less marked, the fingers have become smaller and decreased in diameter, the skin has become tight and smooth and it has lost much of its normal wrinkling. The fingers show mild flexion deformities (Fig. 6).

Roentgenograms of both hands at age of 52 show marked enlargement of the proximal ends of all distal phalanges and bulbous swelling of the distal ends of the second phalanges. There is irregular spur formation. The joint surfaces are distorted and uneven, the joint spaces are decreased in width. Because of flexion deformities they seem to have disappeared entirely in places. Roentgenogram 15 months after the stroke shows a marked demineralization throughout all bones of the left or paralyzed hand but the size, shape and outline of the bones remain absolutely unchanged (Fig. 7).

Case Summary. A 53 year old woman with well-developed Heberden's nodes in both hands was observed before and 15 months after a left-sided hemiplegia. A comparison of photographs and Roentgenograms of the hands before and after the

stroke show that the Heberden's nodes became much less marked and prominent than they had been before. This apparent recession of the process was due entirely to shrinkage of the skin and subcutaneous tissues because the size and contour of the bones remained unchanged, although marked demineralization had occurred.

Discussion. The idiopathic Heberden's nodes affecting multiple fingers of both hands occur spontaneously in susceptible people after middle life. It was formerly

if the patient had been well and pursuing a normal life. It is now known that hard work or injury is not necessary to explain the occurrence of Heberden's nodes.

Heberden's nodes are typical manifestations of degenerative joint disease. The question arises as to whether the observations of this study have any significance in relation to degenerative joint disease in other parts of the body. Degenerative joint disease usually occurs in middle or later life and is thought to be due to deficient or decreased circulation. Experi-



FIG. 6.—Mrs. C. C. The left hand before and 15 months after her stroke. Before, there was marked enlargement of all the terminal interphalangeal joints with flexion deformity and deviation of the index and little fingers. After the stroke enlargement of the joints has become less marked, the fingers are decreased in diameter, the skin looks tight and smooth. The fingers show mild flexion deformities.

believed that they developed in hard-working people in response to exposure of the hands to water or to injury. With this thought in mind, the failure of Heberden's nodes to develop in the injured or paralyzed hand was attributed to lack of use and exposure to injury of that hand. Development of the lesion in the functioning hand was explained as due to increased use. It is readily apparent that the normal hand remaining for use by hemiplegic patients is less exposed to injury than it would have been

mental support to this theory has been presented by Goldhaft, Wright and Pemberton.⁴ They produce bone proliferation and spur formation in the patellæ of dogs by surrounding this bone with mattress sutures, thus interfering with the circulation to this bone. The prevention of Heberden's nodes described here has been associated with a nerve injury or a lesion in the central nervous system affecting the vasomotor mechanisms in the paralyzed areas. This caused increased blood

circulation to bone and resultant osteoporosis.

Demineralization of bone is found in both upper and lower motor-neurone disease, being diffuse in the former and localized in the latter. Both these types of nerve lesions are accompanied by trophic changes in the affected part. Such changes consist of marked altera-

tions in skin temperature, skin color, local circulation, sweating and loss of normal skin markings. There is shrinkage of the limb due to atrophy of subcutaneous tissues, a lead pipe stiffness of the joints, pain on passive motion or pressure and fibrous ankylosis of the joints. The bones themselves show marked osteoporosis and alteration in bone structure although

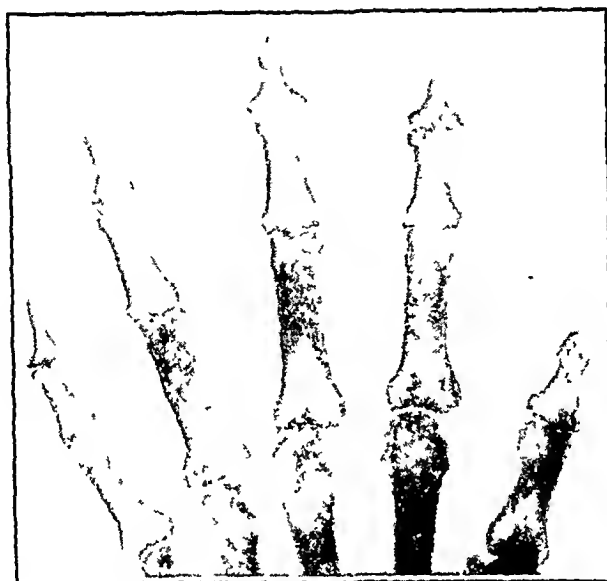


FIG. 7.—Roentgenograms of the left hand before the stroke show enlargement of the proximal ends of all distal phalanges and bulbous swelling of the distal ends of the second phalanges. There is irregular spur formation. The joint surfaces are distorted and uneven, the joint spaces are decreased in width. Roentgenogram after the stroke shows marked demineralization of all bones but the size, shape and outline of the bones remain unchanged.

the joint surfaces retain their normal contour and normal joint space is preserved. Osteoporosis occurs very early in response to disuse even in normal limbs where no trophic soft tissue changes occur. The French clinicians who studied "hemiplegia sans arthritis" argued that the demineralization process, whatever its cause, was the factor which interfered with the development of joint disease.^{2,4}

The osteoporosis is only one of many responses to vasomotor disorder in a paralyzed limb. de Takats¹¹ is of the opinion that several apparently different entities in medical literature based on vasomotor disturbance are essentially one and the same phenomenon. He believes, therefore, that Weir Mitchell's causalgia, Sudek's atrophy, Leriche's post-traumatic painful osteoporosis, the peripheral trophoneuroses of Zur Verth and the chronic traumatic edema of Klassen are slightly different manifestations of a fundamental vasomotor irritability due to damage either to peripheral nerves, spinal cord or cerebral centers. He conceives of 3 stages in this morbid process: (a) An acute painful phase during which the limb is warm and dry and is sensitive to jarring, air currents and emotional upsets. The subcutaneous and periarticular spaces are edematous, muscles are spastic and oscillographic curves indicate increased circulation. Osteoporosis only appears after 4 or 6 weeks of such hyperemia. (b) A second stage when the part is not so warm, and actually may become hard, cyanotic and cold to touch; the joints are stiff and spotty atrophy of bone becomes evident. (c) A final stage of general atrophy of skin, muscle and bone with ankylosis.

de Takats is further of the opinion that the offending vasodilatation cannot be due to sympathetic efferent fibers and attributes the peculiar, painful and trophic disorders to an irritation of the so-called nociceptive fibers of Lewis⁶ in the posterior root system which are capable of secreting a pain substance at their distal terminations. It is further assumed that

such irritation can occur at any of the 3 sensory levels of the nervous system and therefore trophoneuroses and bone atrophy can be found in peripheral nerve injury, poliomyelitis and cerebral thrombosis. This assumption appears to have adequate support in these case presentations where osteoporosis and a concomitant failure of development of Heberden's nodes was found in lesions of nerve trunks, the spinal cord and the gray and white matter of the cerebrum.

The trophic disturbances described above following identifiable injury to the central nervous system led to increased circulation to the limb, demineralization of bone and protection against the development of Heberden's nodes. These conditions must be clearly differentiated from other trophic disturbances of bone leading to neurogenic arthropathy or Charcot's joint. In the latter instance the lesion causes a loss of deep pain sense plus an associated hypotonia of the muscles manipulating the joints. Use of such a hypotonic limb unprotected by pain sense causes serious tissue trauma. It is not clear why such a set of circumstances results in marked bone proliferation, bone destruction and foreign body formation in and about the joint. There is no generalized osteoporosis as invariably occurred in the previous conditions.

Summary. Idiopathic Heberden's nodes (common manifestations of degenerative joint disease) usually involve fingers bilaterally. Nerve injuries of different types may interfere with their development. Three cases of our own are described and 9 cases from the literature are discussed. It was found that peripheral nerve injury, infantile paralysis and stroke prevented the development of Heberden's nodes in affected fingers, though they developed to an advanced degree on the unaffected hand. Such nerve lesions invariably caused osteoporosis which was presumably due to increased blood circulation. Once Heberden's nodes are established, subsequent

cerebral apoplexy causes an apparent regression of the nodes due to shrinkage of soft tissues without alteration in the contour of the bones. Trophic disease pre-

venting the formation of Heberden's nodes must be differentiated from another type of trophic disturbance leading to neurogenic arthropathy or Charcot's joints.

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THE INDICATIONS FOR IRRADIATION OF THE PITUITARY GLAND IN PATIENTS WITH ARTERIAL HYPERTENSION*

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In an earlier publication, Pendergrass, Hodes and Griffith¹ described a bioassay method for detecting an antidiuretic substance in human serum. They considered that this substance originated, in all probability, in the pituitary gland and could therefore be regarded as evidence of increased pituitary activity. Irradiation of the pituitary was carried out in a number of patients who had evidence of such increased activity and, in addition, clinical conditions which might be the result of such increased activity. In this group there were 31 patients with arterial hypertension, 24 of whom had an adequate follow-up. Five patients showed definite improvement in blood pressure and symptoms, 8 showed subjective improvement only, and 11 were not benefited. In the present study a larger number of hypertensive patients were studied, treated and followed for a longer period. Also, certain additional data have been collected with the intention of improving selection of such patients.

The historical aspects of pituitary irradiation have been reviewed previously.¹ Certain additional points, however, should be stressed: (1) In clinical hypertension due to increased activity of the pituitary gland, it is probably the excessive secretion of the pressor hormone that is at fault. Moreover, the pressor hormone is usually, and perhaps always, associated with the antidiuretic hormone. While

there is no satisfactory bioassay method for the pressor hormone, one for the antidiuretic hormone is available. For clinical purposes, therefore, it may be assumed that subjects with hypertension who show increased production of antidiuretic hormone also have an excess of pressor hormone. If such is not always the case, it may supply one reason why pituitary irradiation is not always effective. On the other hand, there is ample evidence that antidiuretic hormone may be present without pressor hormone, or, at least, some individuals with positive bioassays for antidiuretic hormone have perfectly normal blood pressure, as witness patients with premenstrual edema.¹ (2) Antidiuretic substance may be present in the serum of a man or animal without the subject showing antidiuresis after water ingestion. The explanation for this is uncertain, but it may depend upon the development of a refractory state or the production of an opposing diuretic substance, as previously considered by Griffith, Kimbrough, Corbit and Roberts.² (3) Antidiuretic substance may originate elsewhere than in the pituitary, as described by Walker.³ However, when the antidiuretic substance disappears from the serum of patients 1 to 2 months after pituitary irradiation, it appears likely that it can be regarded as being of pituitary origin.

* Except for an occasional revision, this material was presented in the Scientific Exhibit, September 1944, of the American Roentgen Ray Society and the Radiological Society of North America, Inc., where it received the first award.

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Material and Methods of Study. All patients treated were adults suffering from arterial hypertension. In all, 142 subjects received roentgen therapy, 62 males and 80 females. However, adequate follow-up was secured on only 93 patients, and only these appear in the charts. The follow-up period ranged from 3 to 56 months, averaging 16 months. The few patients with the short follow-up period of only a few months invariably represented very ill patients whose results following therapy were poor and who could not return for later studies. If all patients with a follow-up period of less than 6 months had been eliminated, however, the results of therapy would have appeared better than they were. As for age, the middle decades are best represented, 47% of the women being between the ages of 40 and 50, and 44% of the men between 50 and 60.

Methods of Study. 1. Bioassay for anti-diuretic hormone in serum. This was initially positive in all cases that were treated, and was the primary basis for selection. The technique is unchanged from that previously described.¹ Bioassays were repeated at monthly intervals for 3 months after irradiation and thereafter, when possible, every 3 to 6 months.

2. Roentgenograms of the pituitary fossa, in most cases.

3. In some cases, bioassay for gonadotropic hormone, presumably originating in the anterior lobe of the pituitary, at the level of 330 m.u. per 100 cc. of serum, by the mouse method of Rakoff.⁴

4. Measurement of renal function, in most cases, by the plasma creatinine method of Steinitz and Turkand.⁵

5. Measurement of cutaneous lymphatic flow, in most cases, by the patent blue method of McMaster.⁶ This was selected because in the rat increased flow can be demonstrated by this method following the ingestion of water and the administration of an antidiuretic dose of pitressin.

6. Measurement of cutaneous capillary reactivity by direct observation under the capillary microscope, by the method described by Griffith, Roberts and Corbit.⁷

7. Roentgen study of the urinary tract with the aid of diodrast or neo-iopax. This study is suggested because one can obtain additional evidence about individual kidney function. Likewise silent stones and unsus-

pected kidney lesions of significance occasionally are found.

Technique of Roentgen Therapy. Since the previous publication, the tendency has been to use larger doses. While it will be seen in Table 4 that doses have been used varying from less than 1000 to 2000 R in air, and some good results have been achieved with low doses, the higher dose is preferred and 49 of the 93 cases here reported were treated by it. The factors used at the present time are: kilovoltage, 200; milliamperage, 15; filtration, 0.5 mm. Cu plus 1 mm. Al added; half-value layer, 1 mm. Cu; type of machine, constant potential, oil-cooled; roentgens per min., 68.7; target-skin distance, 50 cm.; number of portals, 2; size of portals, 9 cm. diameter; site of portals, lateral temporal, directed at the pituitary fossa; daily exposure, 50 to 200 roentgens to 1 portal; time of administration, 12 days; total exposure, 2×1000 roentgens in air.

RESULTS. It will be seen in Tables 1, 2 and 3 that slightly less than half the patients treated had a significant lowering of blood pressure, and slightly more than half showed appreciable clinical improvement. There is a good correlation between treatment and change in systolic and diastolic blood pressure, and between change in blood pressure and clinical improvement. The material is further broken up into 9 groups as shown in Table 4, where the best results are indicated in the columns on the left and the worst in the right-hand columns. However, it should be noted that in the ninth group only can one be certain that no benefit was obtained, and it is this group that deserves further analysis so that such cases in the future would be either not treated, or treated differently. It is apparent from the upper part of the table that the principal finding, associated with failure of therapy, is failure of the bioassay for antidiuretic hormone to become negative. This might suggest incorrect diagnosis except that it occurs less frequently when larger doses of irradiation are given, and, recently, we have undertaken a second similar course of irradiation within 3 months of the first course, if,

TABLE 1.—EFFECT OF PITUITARY IRRADIATION UPON BLOOD PRESSURE

		(a) Systolic Blood Pressures Before Irradiation				
		Over 250	200-250	170-200	150-170	Below 150
Systolic Blood Pressure After Irradiation	Over 250	4				
	200-250	1	24			
	170-200	..	11	16		
	150-170	..	(7)	8	5	
	Below 150	..	(11)	(6)	5	
		(b) Diastolic Blood Pressure Before Irradiation				
		Over 140	120-140	110-120	100-110	Below 100
Diastolic Blood Pressure After Irradiation	Over 140	14				
	120-140	1	20			
	110-120	..	6	11		
	100-110	(1)	(5)	6	6	
	Below 100	..	(10)	(9)	(4)	

Numbers refer to number of patients. Those in parentheses are thought to show good results and those italicized fair results.

TABLE 2.—CORRELATION BETWEEN CHANGE IN SYSTOLIC AND IN DIASTOLIC BLOOD PRESSURE FOLLOWING PITUITARY IRRADIATION

		Systolic Blood Pressure Change		
		Good	Fair	No change
Diastolic Blood Pressure Change	Good	21	7	1
	Fair	1	12	
	No change	2	1	48

TABLE 3.—CORRELATION BETWEEN CHANGE IN SYSTOLIC BLOOD PRESSURE AND CLINICAL IMPROVEMENT

		Systolic Blood Pressure Change		
		Good	Fair	No change
Clinical Improvement	Definitely good	17	7	6
	Probably good	6	10	12
	No change	1	3	31

TABLE 4.—FACTORS INFLUENCING THE RESPONSE TO PITUITARY IRRADIATION IN HYPERTENSION

	Group No.:	1	2	3	4	5	6	7	8	9
After treatment, bioassay antidiuretic hormone became										
Negative		17	7	5	10	6	1	7	2	10
remained										
Positive		1	5	1	21
Before treatment, bioassay for gonadotropic hormone										
at 330 m.u.:										
Negative		9	5	2	7	2	..	6	1	14
Positive		1	1	5
Before treatment renal function:										
Normal		10	6	2	6	2	..	5	2	16
Abnormal		..	1	..	1	2	1	7
Before treatment cutaneous capillary reactions:										
Normal		11	3	3	7	1	1	3	2	16
Abnormal		4	1	..	3	1	..	4	..	9
Before treatment cutaneous lymphatic flow:										
Normal		6	4	2	6	5	..	2
Abnormal		6	1	3	4	1	1	6	3	5
Roentgen dosage:										
2000 R or more		10	6	2	7	1	..	5	1	17
1500-1990 R		4	..	2	1	3	1	3	2	7
1000-1490 R		3	..	1	..	2	..	3	..	4
Under 1000 R		..	1	1	2	1	..	3
"Selected" cases:										
(a) Renal function normal, gonadotropic hormone										
absent		8	4	2	5	2	..	3	1	10
(b) As (a) but only cases where AD became nega-										
tive after treatment		8	4	1	4	2	..	1	..	4

after that interval, the test for antidiuretic hormone remains positive.

It is apparent also, in Table 4, that persons with renal failure, or with a high titer for gonadotropic hormone in the serum, are apt to do badly after irradiation. While there appears to be a tendency for patients with normal capillary reactions to do better than those with abnormal reactions, and for those with increased cutaneous lymphatic flow to do better than those with normal flow, the tendency is not sufficiently marked to be useful in selection. The last section of Table 4, under (a), shows that by selection of patients on the basis of a positive bioassay for antidiuretic hormone, normal renal function, and a normally absent bioassay for gonadotropic hormone, one should reduce the group of complete failures (Group 9) to 38%, and if one further eliminates the group given an insufficient amount of irradiation (which is the best explanation for the group where the bioassay does not become negative) the group of complete failures (b) would appear to be only 16%, based upon the small series that remain.

The pituitary fossa was enlarged in 7 of 28 cases. This did not seem to bear any relationship to the result of therapy. Where the fossa was enlarged, a pituitary tumor was suspected and in certain instances, the roentgen ray dosage was increased.

Complications of therapy, except for the routine hair loss, did not occur in subjects who did not have papilledema. However, 5 patients with papilledema were treated, and 3 of the 5 showed a fairly characteristic reaction. About 6 hours after the first treatment a severe headache would develop, and this, in a few hours, would be followed by stupor, or delirium, finally coma and convulsions, from which the patient could be partially aroused by lumbar puncture with withdrawal of fluid to relieve pressure, and by hypertonic glucose given intravenously. The following morning the patient would appear to be quite normal and usually had no clear

recollection of the previous evening. Irradiation was continued, cautiously, and subsequent reactions did not occur. This crisis is thought to be due to a choroid plexus hyperemia, with increased formation of cerebrospinal fluid. It is, therefore, important that all patients who present papilledema be hospitalized during treatment. Since none of our patients with papilledema has shown a complete recovery after roentgen therapy, its routine use under these circumstances is not recommended; however, 1 woman did have a remission in which her papilledema subsided, the symptoms cleared and, although her blood pressure did not reach normal, she was much improved and able to do the work for her large family for 5 years, or until 6 months before her death in uremia.

Following irradiation, there has been no evidence of hypopituitarism. Electroencephalographic studies were carried out in 12 patients who had received a total roentgen dosage ranging from 430 to 4760 R. Those patients given more than 2000 R had received more than 1 course of roentgen therapy but no evidence of damage to brain tissue was found.

Relapses occurred 13 times in 10 patients, varying from 6 months to 4 years after irradiation, averaging 18 months. Eight patients were given 2 courses of treatment, and 1 patient was given 3.

Summary and Conclusions. Pituitary irradiation as a treatment for high blood pressure was given to 142 patients without untoward effect, although 3 persons with papilledema showed severe acute but transient reactions indicating increased intracranial pressure. Only 93 patients were adequately followed for a period varying from 3 to 56 months, averaging 16 months. About half of these persons showed improvement in blood pressure and clinical condition. All of these individuals were selected on the basis of a positive test for antidiuretic hormone in the serum. From a consideration of other studies and of the results of varying roentgen dosage, it is concluded that the chance of benefit from radiation therapy to the

pituitary in hypertension should be at least 75% if cases are selected according to the following criteria: (1) Positive bioassay for antidiuretic hormone in serum. (2) A roentgen dosage of 1000 R delivered into the hypophysis (2000 R in air), to be repeated in 3 months if the test for antidiuretic hormone in serum has not become negative in that time. (3) A negative bioassay for gonadotropic hormone in serum, at the level of 330 m.u. per 100 cc. of serum. (4) A normal renal function as shown by a plasma creatinine, by the method of Steinitz and Turkand, of 1 mg. % or less. (Presumably a test of urea clearance would be equally satisfactory.) (5) Good clearance of injected dye from each kidney as shown by urography.

Case Reports. CASE 1. Patient, an apparently healthy white male, was first seen Feb. 26, 1941. He was 23 years old, and about a year previously his school physician had discovered his systolic blood pressure was 175. Several similar readings had been obtained. Physical examination was essentially negative except for the blood pressure which, after a week in bed, was 165/100. The usual laboratory studies, including tests for kidney function and urogram, were entirely negative. Bioassay for antidiuretic hormone was positive on 2 occasions. Accordingly, he was given a course of irradiation to the pituitary from September 3 to 11: 5 cm. portals to temporal areas; 710 R (in air) to left temporal portal; 790 R (in air) to right temporal portal. Thereafter, he returned to school, and a report from his physician, October 20, stated that his blood pressure was no more than 150/95. On December 26, bioassay for antidiuretic hormone was entirely negative. Thereafter, blood pressure remained about 140/90, and in March 1944 he entered the army, with a systolic blood pressure recorded as 135. He had no difficulty in carrying out fairly rigorous duties for the next 2 years, and blood pressure was found within normal limits whenever tested. His own physician found a blood pressure of 126/80 shortly after his discharge, in May 1946. The army records included a description of an examination in 1940 when he had applied for reserve officers training in connection

with his college program and had been rejected with a blood pressure of 175. At the separation center the medical officer insisted that some error had been made in confusing the records of 2 different men.

CASE 2. Patient, a white male 37 years of age, was first seen March 3, 1941. For 1½ years his family physician had found his blood pressure ranging about 180/120. However, after several days in the hospital, it fell to 155/100. Physical examination was otherwise essentially negative, and the usual laboratory studies were normal. Bioassay for antidiuretic hormone, however, was positive, and patient was given a course of pituitary irradiation from March 7 to 15: 5 cm. portals to temporal areas; 695 R (in air) to left temporal portal; 805 R (in air) to right temporal portal.

Bioassays for antidiuretic hormone were subsequently negative on April 14, May 16, June 27, September 8 (1941), and Feb. 6, 1942, and on the same dates blood pressure was 140/90, 138/88, 136/90, 130/82, and 138/90. His own physician has measured his blood pressure half a dozen times a year since, and states that it has never been over 138/90, and is usually 10 to 12 points lower.

CASE 3. Patient, a white male 47 years of age, was first seen Oct. 24, 1945. He complained of some palpitation, and dyspnea during coitus. Hypertension had been discovered 3 months previously, and 9 months previously he had successfully passed a physical examination for aviation pilot. Physical examination, however, in our laboratory revealed a blood pressure of 200/128 and cardiac enlargement. Bioassay for antidiuretic hormone was positive and plasma creatinine was 1.3 mg. % (top normal by this method 1 mg. %). Roentgen ray examination of pituitary fossa, gall bladder, urogram was essentially normal. Electrocardiogram revealed sinus rhythm with ventricular extrasystoles, broad and enlarged P waves, and a slurred QRS complex with left axis deviation. Orthodiagram showed cardiac enlargement. Urinary specific gravity was 1.016 without attempt at concentration. Although it was recognized that patients with renal damage usually do badly after pituitary irradiation, the only evidence suggesting renal involvement was the slightly elevated plasma creatinine. Accordingly, a course of pituitary irradiation was given November 26 to December 7: 7 cm. portals

to temporal areas; 1050 R (in air) to left temporal portal; 1000 R (in air) to right temporal portal.

On Jan. 8, 1946, patient stated he felt much better, had no more palpitation and very little dyspnea during coitus. Blood pressure was 182/128, bioassay for antidiuretic hormone was negative but plasma creatinine was 1.7 mg. %. On February 19 patient still felt well, blood pressure was 186/104, bioassay for antidiuretic hormone was negative, and plasma creatinine was 1.8 mg. %. On April 17 he was definitely worse, with nausea and nocturnal dyspnea, blood pressure 186/118 positive bioassay for antidiuretic hormone, and plasma creati-

nine of 2.2 mg. %. On June 20 he was hospitalized with a blood pressure of 196/118, negative bioassay for antidiuretic hormone, and plasma creatine of 3.9 mg. %. Subsequent course was downhill, and he died with typical uremia on July 7. At necropsy, the heart was found to be markedly enlarged, with left ventricular hypertrophy. There was passive congestion of the liver and spleen and diffuse pulmonary edema. The kidneys were described as being of the granular hypertensive type but were not markedly contracted and the pathologist felt there was less cortical atrophy than might have been anticipated. The urinary tract showed no evidence of infection or congenital anomaly.

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FURTHER STUDIES ON THE CORRELATION OF CHEMICAL STRUCTURE AND ANTITHYROID EFFECT

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THE early clinical experiences with thiouracil indicated that serious toxic reactions sometimes occurred and this prompted an investigation, beginning in 1943, of other antithyroid compounds. It was hoped that the incidence and severity of the toxic reactions might be reduced by obtaining compounds with stronger anti-thyroid action, thereby exposing the body tissues to a smaller concentration of the drug, or by finding substances which by their difference in chemical structure were less toxic than thiouracil even though their concentration in the body might be greater. During the course of these studies there have appeared reports of similar studies by McGinty and colleagues,^{4,8,9}

and Astwood's investigations¹ have been greatly extended.² In addition to the compounds which we have reported upon¹¹ others have been investigated.^{5,6,7}

PLAN OF STUDY. In his early studies Astwood¹ found that most of the compounds with pronounced goitrogenic effect were derivatives of thiourea or aniline. Most of the compounds* which we have studied have been of these types, there being numerous alterations in the structure of the molecules. In addition, a few organic sulfur compounds were tested. The basic structure of some of the more interesting compounds which have been tested in this and in previous studies are shown structurally in Figure 1.

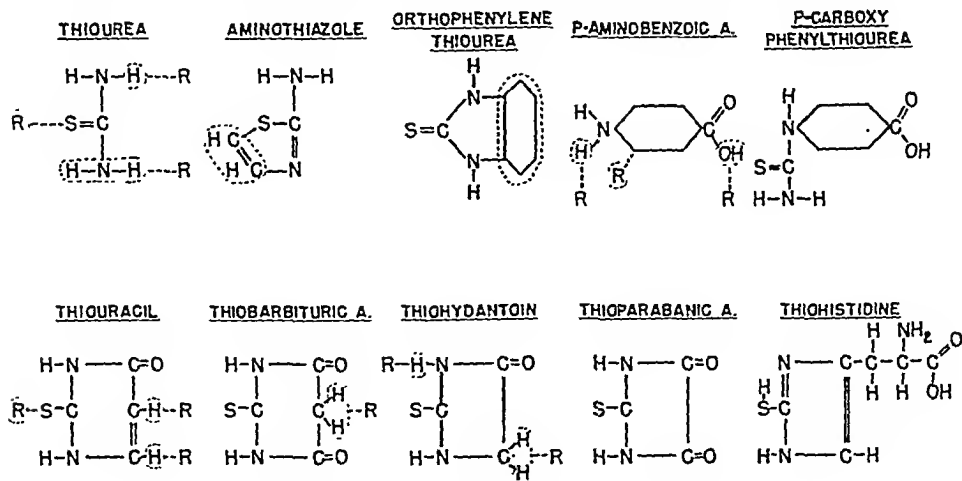


FIG. 1.—Basic structure of some of the interesting compounds studied.

* We are very grateful to Mr. W. A. Lott and the late Dr. George A. Harrop and their associates at the E. R. Squibb & Co., New Brunswick, New Jersey, for supplying us with most of the compounds tested and for aid in many other ways. Dr. R. A. Harte of the Arlington Chemical Company, Yonkers, New York, kindly supplied a few of the chemicals which were tested. Dr. R. O. Roblin, of the American Cyanamid Company, Stamford, Connecticut, supplied the 6- α -ethylpropyl-2-thiouracil.

It was especially desirable to test the antithyroid effect of iodinated thioureas and iodinated aminobenzenes. It was hoped that the thyroid gland's usual affinity for iodine would prevail in this instance and as a result of the high concentration of the antithyroid agent it would be unnecessary to expose the remainder of the body to large amounts of the compound. At the same time there was full realization of the fact that the usual mechanisms of fixation of iodine in the thyroid¹⁰ might be antagonized by the thiourea or aminobenzene portion of the molecule. One would not expect a very striking effect in normal animals even though the compound might be practical in thyrotoxic subjects, because normal thyroid glands do not have as much avidity for iodine. Nevertheless, it was regarded as being worthy of a trial. It has not been possible for us to obtain an iodinated thiourea compound without a radical attached to the sulfur; many thioureas lose their antithyroid effect when the sulfur atom bears a substituent.

The detailed methods of study have been described.¹¹ The rats used ordinarily weighed about 40 gm. at the beginning of the experiment. Their healthy littermates gained, on the average, 4 gm. per day. The animals were given the test compounds in the drinking water, great care being taken to avoid wasting. After ingesting the solution for 14 days, the rats were killed and the thyroid gland was quickly removed and weighed.

Since thiohistidine is a natural constituent of the blood, it was especially desirable to determine whether it possessed any antithyroid effect. Although it had been previously studied in rats,¹¹ and had been found to be without antithyroid effect, the quantity available was small. As an additional test animal the chick was used to study this compound. To 10 cc. of 0.2% agar in saline was added 100 mg. of thiohistidine. Each of 3 chicks was injected, subcutaneously, with 0.1 cc. of the mixture twice daily for 14 days, beginning when the chicks were 2 days old. The

animals were then killed, along with the controls, and their thyroid glands were quickly removed and weighed.

RESULTS. Thiouracils. The most potent antithyroid compounds found were thiouracils with short-chain hydrocarbons in the 6-position. Of these, the *n*-propyl derivative was the most active one, and it was also the most effective one found by Astwood, Bissell and Hughes.² Cyclopropylthiouracil and isobutylthiouracil were almost as active as was *n*-propylthiouracil. The effectiveness of *n*-butylthiouracil and amylthiouracil was much less marked, but all of these were distinctly more active than was thiouracil (Fig. 2).

Of the compounds tested with substituents in the 5-position, ethylthiouracil was the only one that was more active than thiouracil. The activity of the 5-ethylthiouracil was abolished when an ethyl radical was attached to the sulfur, as in 2-ethylmereapto-5-ethyluracil (Table 1). When an amino group was in the 5-position the activity was lost.

The toxicity of all of the thiouracils was relatively low. There was no significant inhibition of growth. Moreover, microscopic examination of the liver, spleen, pancreas, kidneys, adrenals and gonads revealed that these organs were normal in appearance.

Other Thioureas. None of this group of compounds tested possessed significant activity, with the exception of 2-aminothiazol (Table 2). The latter compound, although many times less active than thiouracil, produced a distinct effect when large doses were used. Several thioureas were fairly toxic, especially bis-(methylpiperidine)thiourea, 1, 4-diazabicyclo(2,2,-1)heptane and bis-(2-hendeeyl-2-imidazole-1-ylethyl)thiourea.

The chicks, treated with thiohistidine, experienced no thyroid enlargement.

Anilides. Several anilides with structures similar to *p*-aminobenzoic acid were studied (Table 2). The activity of each of these compounds tended to be relatively slight (Table 2), even in large doses. The

TABLE 1.—RELATION OF CHEMICAL STRUCTURE TO GOITROGENESIS

Compound	Formula	Concentration in drinking water (%)	Total amount ingested (mg./100 gm.)	Average weight at death (gm.)	Weight of thyroid (mg./100 gm.)	
					Range	Average
2-Thiouracil	<u>NHCSNHCOCHCH</u> Thiouracils	0.001	2.4	81	6.3-7.1	6.7
		0.002	4.6	107	9.2-10.5	9.0
		0.004	9.4	86	5.5-10.3	8.4
		0.005	14.4	131	7.4-10.8	8.7
		0.005	12.1	80	3.3-6.2	3.8
		0.006	12.9	84	8.1-10.2	8.8
		0.007	17.8	76	8.7-12.5	10.2
		0.008	21.2	91	8.3-10.0	9.0
		0.01	23.8	159	9.1-14.2	11.4
		0.01	23.6	79	11.6-10.4	13.1
		0.01	20.1	84	5.4-11.1	9.1
		0.01	20.4	71	7.1-10.5	8.5
		0.01	24.3	80	4.8-13.2	8.2
		0.01	26.8	104	8.3-11.7	9.7
		0.02	51.6	85	6.3-11.0	8.2
		0.02	35.9	76	6.1-8.0	7.0
2-Thio-5-ethyluracil	<u>NIUCSNHCO(C₂H₅)CH</u>	0.02	46.8	113	14.2-21.1	17.6
		0.04	77.0	88	9.9-19.5	14.1
		0.04	81.0	69	4.6-15.1	9.8
		0.04	86.6	113	13.8-26.6	18.2
		0.05	107.5	70	13.0-13.3	13.2
		0.001	2.2	115	5.8-8.1	7.2
		0.003	6.2	107	8.3-10.7	9.6
		0.005	11.5	118	16.1-20.4	17.2
		0.007	14.8	110	9.7-21.4	16.3
		0.01	16.3	121	12.2-21.1	18.6
2-Thio-5-aminouracil	<u>IIUCSNHCO(C₂H₅)CH</u>	0.02	42.3	123	15.1-18.2	16.1
		0.01	22.9	98	6.0-8.9	7.0
2-Thio-5-phenylacetylaminouracil	<u>NIUCSNHCO(C₂H₅)CH</u> <u>NCSC₆H₅NIUCOC(C₂H₅)CH</u>	0.01	34.3	92	6.0-6.2	6.1
		0.1	235.0	85	3.6-11.7	7.4
2-Ethylmercapto-5-methyluracil	<u>NIUCSNHCO(C₂H₅)CH</u> <u>NCSC₆H₅NIUCOC(C₂H₅)CH</u> <u>NIUCSNHCOCHCHCHONH₂</u>	0.01	21.2	131	7.3-8.3	7.8
		0.0001	0.27	95	6.4-8.2	7.3
		0.0005	1.21	99	6.0-8.0	6.8
		0.001	2.78	126	5.8-8.4	7.3
		0.0001	0.21	97	6.0-9.6	7.7
		0.0005	1.27	118	5.2-10.7	7.6
		0.001	2.7	131	10.0-14.1	12.4
		0.0001	0.23	115	7.5-10.6	8.4
		0.0003	0.75	120	8.9-10.4	9.7
		0.0005	1.2	120	15.2-16.5	15.9
Diethylacetal-2-thio-1-uracil aldehyde	<u>NIUCSNHCOCHCHCH</u> <u>NIUCSNHCOCHCHCH</u>	0.001	2.4	103	7.9-36.4	20.6
		0.003	6.7	122	28.8-35.6	32.7
		0.003	11.9	115	36.2-40.6	37.7
2-Thio-6- <i>n</i> -propyluracil	<u>NIUCSNHCOCHCHCH</u>	0.0001	0.27	95	6.4-8.2	7.3
		0.0005	1.21	99	6.0-8.0	6.8

2-Thio-6- <i>n</i> -propyluracil	$\text{NHCSNHCOCHCHCH}_2\text{CH}_2$	0.0001 0.0003 0.0004 0.0005 0.001 0.003 0.005 0.0003 0.0005 0.0007 0.001 0.003 0.005 0.007 0.01 0.0001 0.0001 0.0002 0.0002 0.0003 0.0003 0.0003 0.0004 0.0004 0.0005 0.0005 0.001 0.001 0.002 0.003 0.005 0.001 0.01 0.0005 0.0007 0.0007 0.001 0.001 0.002 0.002 0.003 0.005 0.005 0.01 0.01 0.003 0.001	0.3 0.8 0.78 1.24 2.4 8.3 9.4 0.80 1.2 1.6 2.5 7.3 10.7 13.7 17.8 0.35 0.30 0.55 0.60 0.65 0.69 0.90 0.95 0.62 0.70 0.96 0.85 0.31 1.27 2.3 2.3 7.3 14.2 11.1 10.4 11.2 19.6 21.6 1.3 1.8 1.6 3.0 2.0 4.6 4.8 6.0 11.1 11.4 11.9 21.0 16.5 0.49 1.9	129 120 125 119 136 131 84 109 127 107 110 113 156 117 74 72 66 65 70 81 71 67 101 99 62 74 120 118 108 90 91 57 74 83 69 113 89 128 120 118 119 108 120 112 112 114 65 122 104 87 102 103	5.3-6.2 6.6-8.9 8.3-9.9 10.0-12.1 9.1-14.8 32.4-34.4 26.1-35.6 7.1-8.8 5.8-8.4 8.3-8.6 8.5-10.9 8.4-14.5 18.6-25.2 10.2-13.1 10.6-17.1 6.3-12.3 6.4-9.4 6.5-14.0 8.8-11.9 7.2-10.6 6.6-9.8 9.0-12.0 5.9-9.9 7.2-7.9 5.8-7.5 6.9-10.3 7.7-11.3 10.8-13.3 10.1-16.5 13.4-15.3 15.3-19.9 25.6-29.6 13.0-16.0 32.1-41.4 16.0-22.7 39.7-47.5 23.8-33.7 30.8-40.1 6.2-8.0 8.5-8.9 6.7-8.8 7.0-8.7 7.3-14.5 7.0-9.1 7.3-10.7 5.3-12.4 9.3-10.2 11.1-14.4 11.4-16.1 12.7-28.4 13.7-24.3 7.8-10.3 8.7-10.0	5.7 7.8 8.9 10.8 11.6 33.3 30.6 7.9 6.9 8.4 9.8 11.5 22.2 11.7 14.5 8.9 7.8 11.0 10.4 9.0 8.2 10.7 8.4 7.5 8.9 9.8 12.3 12.8 14.0 17.5 27.9 14.1 36.4 18.7 43.7 27.7 35.5 7.2 8.6 7.5 7.5 10.3 8.1 9.4 8.8 9.9 12.9 13.6 21.0 19.5 8.9 9.2
2-Thio-6- <i>n</i> -butyluracil	$\text{NHCSNHCOCHCHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$					
2-Thio-6- <i>i</i> -obutyluracil	$\text{NHCSNHCOCHCHCH}_2\text{CH}(\text{CH}_3)_2$					
2-Thio-6- <i>n</i> -amylthiouracil	$\text{NHCSNHCOCHCHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$					
2-Thio-6- α -ethylpropyluracil	$\text{NHCSNHCOCHCHCH}(\text{C}_2\text{H}_5)\text{C}_2\text{H}_5$					

* These tests were conducted on a compound which was first thought to be isomylthiouracil. However, it proved to be isobutylthiouracil. The net result was a comparison of isobutylthiouracil obtained from two different pharmaceutical companies.

toxicity of diaminobenzophenone and p-aminocinnamic acid was fairly great.

Iodinated Compounds. The iodinated compounds demonstrated little or no antithyroid effect. Moreover, several of these compounds were relatively toxic. Three groups of rats receiving 0.5% 2-amino-3,5-diiodobenzoic acid succumbed after treatment for 4 or 5 days. The 4-amino-3,5-diiodobenzoic acid was less toxic and the monoiodinated homologue was much less toxic.

of the various antithyroid compounds. In some instances the substances are relatively much more effective in rats than in humans and sometimes the reverse is true. Moreover, there are occasionally marked variations in the same species. That such discrepancies should exist is indicated by the variations in the absorption, distribution and excretion of the compounds in rats and man.¹²

In some respects there are striking cor-

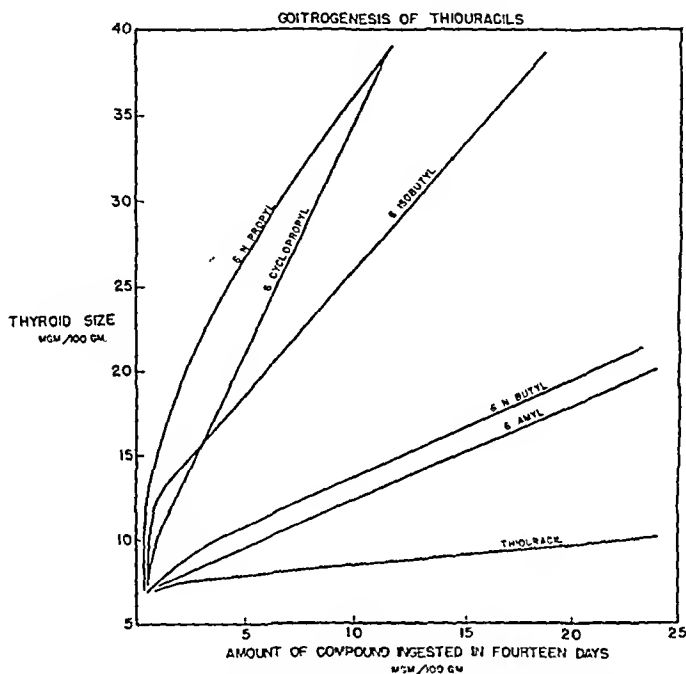


FIG. 2.—Note that these derivatives of thiouracil are much more goitrogenic, or antithyroidal, than is the parent compound. The size of the thyroid gland and the amount of drug ingested are expressed in terms of body weight of the animal.

Combined Treatment With Para-aminobenzoic Acid and Thiouracil. It can be seen in Table 2 that when p-aminobenzoic acid is given simultaneously with thiouracil the amount of goitrogenesis equals, or perhaps exceeds, an additive effect of the 2 compounds.

Discussion. In the clinical application of the results presented in this paper and in previous ones it must be borne in mind that the assays on rats are but coarse approximations of the relative activities

relations of chemical structure to antithyroid effect. However, in many instances slight changes in molecular structure lead to very unpredictable results, sometimes markedly increasing the activity and at other times reducing it.

On the basis of the observations of various investigators, especially Astwood's, many generalizations may be made in correlating antithyroid activity with chemical structure. The activity of thiouracil was distinctly *decreased*, or in some in-

TABLE 2—RELATION OF CHEMICAL STRUCTURE TO GOITROGENESIS

Compound	Formula	Concentration in drinking water (%)	Total amount ingested (mg./100 gm.)	Average weight at death (gm.)	Weight of thyroid (mg./100 gm.)	
					Range	Average
2-Aminothiazol	OTHER THIOUREAS $\text{NH}_2\text{CSCHCHN}$ $\text{C}_6\text{H}_{10}\text{NCH}_2\text{NHCSNHCH}_2\text{NC}_6\text{H}_{10}$	0.1 0.3 0.0005 0.001 0.01 0.01 0.01 0.1 0.01	193.0 464.0 1.5 3.0 234.0 21.0 29.0 280.0 27.4	86 80 87 82 105 109 108 83 86	7.1-11.2 18.5-34.2 6.6-8.2 7.3-8.9 3.8-8.2 6.9-7.1 6.6-8.2 6.3-7.5 7.1-8.5	8.5 25.6 7.4 8.1 5.7 7.0 7.5 6.9 7.6
Bis-(methylpiperidine)thiourea	$\text{C}_6\text{H}_5\text{SNHCSNHCO}$ $\text{NC}_6\text{H}_4\text{CONHC}_6\text{H}_4$ $\text{NH}_2\text{CSNHCH}_2\text{CH}_2\text{CONHC}_6\text{H}_4$ $\text{NC}(\text{CH}_3)_2\text{NC}(\text{CH}_3)_2\text{NCH}_2\text{CH}_2\text{NHC}_6\text{H}_4$ $\text{NC}(\text{C}_6\text{H}_5)_2\text{NCH}_2\text{CH}_2\text{NHC}_6\text{H}_4$ $\text{NC}(\text{C}_6\text{H}_5)_2\text{NCH}_2\text{CH}_2\text{NHC}_6\text{H}_4$ $\text{NHC}_6\text{H}_4\text{CONHCOC}(\text{C}_6\text{H}_5)_2\text{CO}$	0.01 0.01 0.01 0.01 0.01 0.01 0.01	28.6 29.2 299.0	51 64 78	...	4.3 4.6 7.3
1,4-Diazabicyclo(2,2,1)heptane-7-thione	$\text{NHC}_6\text{H}_4\text{CONHCOC}(\text{C}_6\text{H}_5)_2\text{CO}$	0.1	2460.0	63	9.3-17.2	12.4
5-Thienyl-2-thiothiouric acid	ANILIDES $\text{NH}_2\text{C}_6\text{H}_4\text{COOH}$ $\text{NH}_2\text{C}_6\text{H}_4\text{CONHC}_6\text{H}_4\text{COOH}$ $\text{NO}_2\text{C}_6\text{H}_4\text{CONHC}_6\text{H}_4\text{COOH}$ $\text{NH}_2\text{C}_6\text{H}_4\text{CHCHCOOH}$	1.0 1.0 1.0 1.0 0.3 0.3 0.5 0.5 0.1 0.3 0.5	2920.0 2165.0 199.0 657.0 1695.0 1042.0 215.0 625.0 695.0 1127.0	57 63 92 154 28 140 121 72 49 51	4.1-12.6 6.9-9.0 4.4-8.7 6.3-8.8 34.0-58.0 3.3-8.2 6.7-7.6 6.1-9.9 10.5-17.4 7.8-20.5	9.7 7.7 6.3 7.3 47.3 6.3 7.1 8.0 14.3 14.1
p-Aminobenzoic acid	$\text{NH}_2\text{C}_6\text{H}_4\text{COOH}$	0.1	312.0	75	7.2-18.4	11.8
p-Aminobenzoic acid	IODINATED COMPOUNDS $\text{NCS}(\text{C}_6\text{H}_5)_2\text{NHCOCCH}$ $\text{NH}_2\text{IC}_6\text{H}_4\text{COOH}$	0.1 0.1 0.1 0.1 0.5 0.1 0.1 0.1 0.5 0.1 0.1 0.3 0.5 0.5 0.3	259.0 620.0 271.0 1410.0 266.0 624.0 320.0 1810.0 283.0 790.0 1270.0 1100.0 713.0	88 95 86 83 89 97 64 117 100 114 118 98	8.3-8.3 4.7-7.0 3.7-8.1 ... 6.5-9.7 6.9-13.1 7.5-10.0 5.7-9.4 6.1-7.2 6.4-8.9 5.6-6.7	8.3 9.7 6.1 6.8 11.6 8.8 8.3 9.6 8.4 7.8 6.5 7.7 6.1
p-Amino-3,5-diiodobenzoic acid	$\text{NH}_2\text{IC}_6\text{H}_3\text{COOH}$	0.1	29.6	81	9.1-10.2	9.9
p-Amino-3,5-diiodobenzoic acid	$\text{NH}_2\text{C}_6\text{H}_3\text{I}_2\text{SO}_2\text{NH}_2$ $\text{I}_2\text{OHC}_6\text{H}_3\text{CH}_2\text{COOH}$	0.01	1330.0	77	3.9-8.9	7.1
3,5-Diiodosulfanilamide	PARAMINOENZOIC ACID + THIOURACIL NHCSNHCOCHCH $\text{NH}_2\text{C}_6\text{H}_4\text{COOH}$	0.5 0.01 0.5 0.005 0.5 0.005 0.5	25.3 1295.0 11.7 1440.0 12.9 1290.0	75 116 139 142	10.7-19.0 7.2-8.9 7.6-8.2 9.9-10.4	14.4 7.8 8.0 10.1
1-Amino-2-iodobenzene-4-sulfonamide						
3,5-Diiodo-4-hydroxyphenylacetic acid						
2-Thiouracil						
p-Aminobenzoic acid						
2-Thiouracil + p-aminobenzoic acid						
2-Thiouracil						
p-Aminobenzoic acid						
2-Thiouracil + p-aminobenzoic acid						

stances lost, by any of the following changes in structure:

1. Saturation of the double bond, as in dihydrothiouracil.
2. Addition of methyl or ethyl substituents on the nitrogen atoms.
3. The presence of methyl or butyl radicals in the 5-position.
4. The presence of substituents on the sulfur atom.
5. Additions in the 5- or 6-position of amino, carboxy, carbethoxy or cyano groups.

On the other hand the activity of thiouracil was *increased* by:

1. The addition of short-chain hydrocarbons or the benzyl radical to the 6-position.
2. The presence of an ethyl or propyl group on the 5-position. Substituents in the 5 and 6 positions (in 1 compound) showed no potentiation of effect.

The activity of thiourea is augmented by the addition of certain short-chain hydrocarbons, as in diethylthiourea and tetramethylthiourea. On the other hand, in general the activity is greatly decreased or lost by:

1. The addition of long-chain alkyl or aryl radicals.
2. The presence of amino, imino or carbonyl radicals attached to 1 or both nitrogen atoms.
3. Substitutions on the sulfur atom.
4. Conjugation of 2 thiourea molecules.

It is of interest to point out that mere closure of the ring as in phenylthiourea, giving o-phenylene thiourea, greatly increases the antithyroid effect.⁴ In a similar manner the activity of ethylthiourea is increased when the ring is closed to form 2-imidazoline-2-thiol. Addition of iodine to the 5-position of o-phenylene thiourea decreases its activity by about 90%.

One of the nitrogens of thiourea may be replaced with oxygen or sulfur with the preservation of some activity. One example is 2-mercaptothiazoline² which is slightly more active than thiouracil.

Although it has been found that in several instances when the sulfur of thiourea is incorporated in a ring structure the activity is greatly decreased, this is not the case with 2-aminothiazole. It is of interest that when the C=S bond of thiourea is saturated, as in 2-aminothiazole, activity is not lost.²

None of the aminobenzenes has been found to be as active as thiouracil, although 2 have been found² to be one-fourth as active, 4,4'-diaminodiphenylmethane and bis-(4-dimethylaminophenyl)-methane.

Iodination of aminobenzoic acid did not cause any definite potentiation of antithyroid effect.

With the data available it is not possible to state whether p-aminobenzoic acid and thiouracil have a synergistic effect or whether they have a different site of action. However, they do have an additive effect.

Many of the more potent compounds have been given a clinical trial.^{3,13}

Conclusions. Minor structural changes in the 2 main series of goitrogenic compounds, thiocarbonamides and aminobenzenes, may modify the activity of these compounds, sometimes causing a marked potentiation of effect and at other times greatly decreasing or abolishing the effect. The C=S linkage is essential, and usually without substituents attached to the sulfur. In most instances this linkage is adjacent to 2 amino groups, although activity can exist when 1 of the amino groups is replaced by an oxygen or sulfur grouping. Closure of thiourea chains generally causes a potentiation of effect. Additions of short-chain hydrocarbons tend to augment the effect of thiouracil, when attached to the 6-position. Thus far, iodination of the thiourea and aminobenzene derivatives has not augmented the goitrogenic effect. The simultaneous ingestion of thiouracil and p-aminobenzoic acid appeared to result in an additive effect.

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POSTHYPOGLYCEMIC ENCEPHALOPATHY

CASE REPORTS

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THE clinical entity, posthypoglycemic encephalopathy, has been previously reported under headings of synonyms such as fatal hypoglycemia,⁴⁰ mental deterioration associated with convulsions and hypoglycemia,¹¹ cerebral damage from insulin shock,¹ irreversible or hyperglycemic insulin coma,⁵⁰ prolonged coma after insulin hypoglycemia,³³ fatal hyperinsulinism with cerebral lesions due to pancreatic adenoma,²³ posthypoglycemic coma or syndrome,¹⁸ and psychiatric complications of hypoglycemia in children.²

Even before the introduction of insulin, Joslin²² recognized that hypoglycemia was a very serious factor in the treatment of diabetes. Wohlwill⁴⁹ in 1928 made the first detailed study of brain changes in a diabetic dying from insulin shock, and in the same year Ravid³⁷ summarized 6 cases of transient hypoglycemic hemiplegia reported in the literature to that date including a case of his own. In the first case of benign tumor of the islands of Langerhans with hypoglycemia proved by antemortem blood studies, reported by McClenahan and Norris,³² there were evidences of meningeal and cerebral irritation on postmortem examination. Carr,⁹ in 1931, reported the case of a diabetic patient with hemiplegia for many weeks after hypoglycemia, and Bast, Schmidt, and Sevringhaus,⁶ in 1932, reported a case of hypoglycemia with neurologic symptoms persisting for 5 days after adequate feeding was instituted. At the same time Terplan⁴³ reported the case of a 16-year old diabetic boy who did not regain consciousness for 3 days after insulin shock, the blood sugar levels being normal for these 3 days. Postmortem examination showed extreme edema of the brain and destruction of ganglion cells. Wilder⁴⁷

wrote: "A feature about this type of coma (hypoglycemia) that is very characteristic is its rapid termination when glucose is administered—but recovery is less certain, less rapid and less complete, even when sugar is given, the longer it persists. Irreversible changes may then occur in the brain: degeneration of the ganglion cells, or hemorrhages as described by Terbrüggen." Since that time numerous reports of the same clinical entity have appeared in the literature.

With this introduction, 2 cases personally seen by the author and one other case will be reported:

Case Reports. CASE 1: M. J. W., a 26 year old white male, was first seen at his home on Sept. 8, 1943, at 6 p. m. He had been a known diabetic for 4 years, taking 50 units of protamine zinc insulin daily and not adhering to any special diet. He had had several mild insulin reactions during the preceding two weeks. The day before he was seen he changed his working hours to the midnight to 8 a. m. shift. As his wife worked in the daytime she did not see him at all on Sept. 8th until she returned home at 5.30 p. m. and found the patient lying on the floor, unconscious. The eggs he ordinarily cooked for himself for breakfast were burned to a crisp, and the gas fire beneath them was still burning. It was not known whether he took his insulin that morning.

Examination revealed a young adult white male lying quietly in bed (having been placed there by his wife), perspiring profusely, and unresponsive. Pulse was 88; respirations, 20; blood pressure, 110/86; and temperature, 101.0°. Pupils were dilated and there was normal intraocular pressure to palpation. Teeth were occasionally grinding together. There was no fruity odor to the breath, and the skin was warm and moist. There was carotenemia with a yellowish color to the palms of the hands. Otherwise, a complete

physical examination revealed no abnormality.

The patient was given 30 cc. of 50% glucose intravenously and responded enough to drink about 100 gm. of sugar in solution. In spite of this, his movements became irrational and meaningless and he lapsed back into a stupor. When he was conscious enough to drink he was not able to answer questions or make any meaningful sounds. He was admitted to Baylor University Hospital at 8 p. m. Blood sugar at that time was 460 mg. per 100 cc. and the CO_2 combining power was 40 volumes %. While these results were pending, the patient was given another 125 cc. of 50% glucose intravenously and continuous intravenous glucose was started. The patient became quite unruly and violent, struggling constantly, having to be restrained, and pulled out the intravenous needle after only 300 cc. of 5% glucose had been administered. However, the patient drank 700 cc. orange juice during the night. He continued to be irrational, had occasional mild convulsive seizures, and was frequently mumbling, restless, and trying to get up. Temperature went as high as 102.8° axillary and pulse up to 120/minute.

The 8:30 a. m. blood sugar level on Sept. 9th was 420 mg., and the CO_2 combining power 56 volumes %. Because of the high blood sugar levels the patient was given insulin then for the first time, 25 units of protamine zinc insulin and 15 units of regular insulin, in separate syringes. The patient consumed 1500 cc. orange juice with 60 gm. glucose added and 240 cc. milk orally between then and 3:30 p. m. when his blood sugar level was again determined and said to show no trace of glucose (checked). There was no change in the clinical course during this interval except that the patient screamed irrationally at times. He voided involuntarily. Juices and milk were continued orally and a 9 p. m. blood glucose level was 470 mg. Blood sugar levels checked frequently during the next two days varied from 250 to 460 mg. The patient was given 25 units protamine zinc insulin on each of the next few mornings and he continued to have an adequate carbohydrate intake. He continued to be restless, drowsy, uncooperative, and mentally confused for two more days. When he was finally rational on Sept. 12th, he could not recall anything that had happened for the 24 hours prior to the time he was first seen.

Thereafter the patient improved and apparently had an uneventful course after proper regulation of his diabetes.

CASE 2. T. A. C., a 55 year old white male, had been a known diabetic since 1938. As he was a bachelor he ate in cafes and remained on no specific diet. He usually took 40 units protamine zinc insulin daily but had decreased his insulin and had been drinking wine prior to being admitted to St. Paul's Hospital in diabetic coma on Feb. 13, 1945. He responded to therapy quite satisfactorily and was instructed on a 3000 calorie, 200 gm. carbohydrate, 100 gm. protein diet, to include a feeding of 30 gm. of carbohydrate before retiring each night. The importance of maintaining the carbohydrate consumption at a constant level was stressed, the patient being kept in the hospital until Feb. 27th in order for him to learn as much as possible about his diabetes, which was well regulated with 60 units protamine zinc insulin and 15 units regular insulin in separate syringes before breakfast daily. His fasting blood sugar level was 90 mg. on the day prior to discharge from the hospital. Because it was believed that the patient possibly would not properly follow his diet, his insulin was decreased to 50 units protamine zinc insulin and 10 units regular insulin on Feb. 26th and 27th. He was discharged on this regimen, having been given diet lists and taught equivalent carbohydrate measures.

In spite of his careful diet instructions it was later learned that he ate only a bowl of soup for his evening meal on Feb. 27th. At 3:00 a. m. on Feb. 28th his landlady heard him making peculiar noises in his room. She entered his room at 7:00 a. m. and reported that he was apparently "normal" at that time. Whether he ate breakfast or took insulin that morning was unknown, but at 10:00 a. m. he was found lying on the floor of his room, unresponsive.

When the patient was seen at 11:00 a. m. he was still unconscious, perspiring excessively. Temperature was 104.0° ; pulse, 130; respirations, 28; and blood pressure, 110/60. Pupils were quite irregular in contour, the patient previously having had bilateral cataract extractions. There was excessive salivation, much mucus seemed to be in his throat, crepitant râles and coarse rhonchi were heard throughout both lung fields, and

the patient seemed to have occasional fine tremors over his body.

The patient was given 25 gm. of glucose intravenously but failed to show any response. He was readmitted to St. Paul's Hospital at 12:00 noon on Feb. 28th. As the laboratory technician was not available for blood sugar determination without some delay, 10% glucose solution was started intravenously immediately upon his arrival and was continued until the patient had received 4000 cc. by 10:45 p. m. At 2:30 p. m. the blood sugar level was reported as 164 mg. per 100 cc. The patient was given no insulin and the 8:00 a. m. blood sugar level on March 1st was 53 mg. At 6:00 a. m. on March 1st, nurses recorded that the patient turned himself with ease but was generally unresponsive. As the patient remained unable to swallow, he was given 1000 cc. 10% glucose intravenously at 8:00 a. m., 12:00 noon, and 6:00 p. m. daily, and 1000 cc. 5% glucose intravenously at 12:00 midnight each day thereafter. It was learned that on this program he required and was given only 15 units of protamine zinc insulin daily. Daily 8:00 a. m. blood sugar levels thereafter varied from 74 to 346 mg. Because of the fever and pulmonary edema the patient was given 5 gm. of sodium sulfadiazine intravenously daily. The temperature returned to normal and the lung fields became normal upon examination by March 6th. The patient remained semicomatose on March 1st until 9:00 p. m., at which time he appeared very restless, got out of bed, struggled with the nurses, and had alternating intervals of crying out irrationally and of being quiet. This type of behavior occurred intermittently throughout the night. The patient was incontinent of urine and feces throughout the remainder of his hospital course. He lapsed back into a semicomatose condition on March 2nd and occasionally signified feeling pain when stuck with a needle. On some occasions thereafter he was seen to move his right arm and his right leg but very seldom moved his left arm or left leg. He occasionally mumbled unintelligible sounds and occasionally shook his right arm and fist as if an orator trying to say something. He made occasional grimacing motions and was mentally dull and apathetic throughout his hospital stay. He occasionally coughed but was unable to expectorate, swallow, or speak.

Neurological examination revealed normal triceps, biceps, patellar, and ankle jerk reflexes on the right. Left ankle jerk and patellar reflexes were present but diminished, and the biceps and triceps reflexes were missing on the left. Babinski sign was positive bilaterally. There was no evidence of any cranial nerve involvement. The patient was unable to carry out any command. The heart and vessels were normal except for some tortuosity of the brachial arteries. Abdomen, back, genitalia, rectal examination, and extremities were normal.

On March 5th lumbar puncture revealed clear colorless spinal fluid with pressure of 14 mm. of mercury and no evidence of spinal block. Wassermann and colloidal gold tests were negative and globulin content was normal. White blood cell count was 15 and red blood cell count was 37 per cubic mm. spinal fluid. On March 1st hemoglobin was 11.9 gm. per 100 cc. blood, and white blood cell count 11,000 per c.mm. with a normal differential count. On March 5th, hemoglobin was 10.6 gm. and white blood cell count 7,050 with a normal differential count. Urinalyses were normal except for occasional glycosuria and a terminal pyuria after the patient was catheterized.

The patient remained about the same until March 16th when he became weaker, his temperature began rising, and signs of pneumonia appeared in the lungs. He died on March 18th at 8:20 p. m.

Postmortem examination, as reported by Dr. J. L. Goforth, revealed nothing abnormal externally other than decubitus ulcers in the sacral region. There was marked congestion in the posterior portion of each lung with patchy areas of consolidation noted, grossly suggestive of aspiration pneumonia. Heart examination revealed some dilatation of the right auricle and ventricle, and the left ventricle was fairly well contracted. There were no other gross pulmonary or cardiac abnormalities. No gross nor microscopic abnormality was found in the gastrointestinal tract. The urinary bladder mucosa had an injected appearance, the retention catheter being in place, but there were no other gross abnormalities of the kidneys, prostate, liver, gallbladder, spleen, or lymph nodes. The medullary portion of each adrenal showed what was interpreted as postmortem degeneration. The pancreas was soft and irregularly lumpy with loss of

glandular tissue apparent and no evidence of tumor formation. The brain had a congested appearance but no other gross abnormality. The pituitary body had no apparent changes.

Microscopically there was a moderate degree of myocardial hypertrophy and acute myocardial degeneration; acute spreading bronchopneumonia and a marked degree of pulmonary congestion and edema; congestion and a moderate degree of hyperplasia of the spleen; a marked degree of tubule cell degeneration in the kidneys; diffuse fine scarring and islet degeneration in the pancreas; cortical degenerative changes in the adrenals; and cortical cell degenerative changes in the brain.

A more extensive examination of the brain as reported by Dr. Paul M. Levin revealed moderate hyperemia of the leptomeninges of the cerebral hemispheres. There was an occasional area in the cortex of brownish discoloration, and in other places the tissue seemed more friable than normal. Several radial areas of softening were seen extending from the pial surface through the cortex into the subcortical white matter. The secondary segments of the globus pallidus on both sides showed blurring of the striation and perhaps slight pallor. The region of the third ventricle was normal, as was the remainder of the brain stem and cerebellum. The white matter of the cerebral hemispheres was slightly hyperemic. In places it showed a diffuse brown discoloration. One area of softening was seen in the left occipital lobe; the lateral surface underlay the depth of the calcarine fissures and was curved in a semi-circular way so as to conform with the fold of the cortex about this fissure. Sections were cut from both motor areas (from the right including the Rolandic vein in a long block and from the left a deeper block with only pre-central and post-central gyri), wall of third ventricle, globus pallidus, frontal pole, calcarine cortex, and cerebellar cortex. The gross diagnosis was mild hyperemia.

Microscopic examination revealed large areas of cerebral cortex with a regular architecture, composition and vascularity, except for a slight pallor of the ganglion cells. However, in numerous areas of considerable size the cortex had a spongy structure with loss of normal lamination and intense congestion of the blood vessels. The ganglion cells in these lesions were greatly reduced in number;

those present were small with pale cytoplasm having an indistinct border. The interstitial cells were greatly increased in number, mostly microglial and phagocytic. Astrocytes were also present in small numbers, often in clumps. These cortical lesions rarely extended deeper than the sixth layer and usually stopped at the fifth; only where they were most severe did the first layer show microglial proliferation. Necrosis was most severe in the third layer where collections of fat-filled phagocytes (glitten cells) were seen; in these areas capillary proliferation was pronounced. The walls of the vessels showed thickening of the walls with endothelial swelling and concentric layers of plump elongated cells. There was also an increase in the number of vessels. The lesions were extensive in the central and occipital cortex, with the least alteration in the frontal poles. The pre-arachnoid was not thickened, but there was a moderate number of macrophages. The globus pallidus showed only a ferruginous deposition in the form of round particles lying in the parenchyma and in walls of blood vessels. The hypothalamus and cerebellar cortex appeared normal. The hypophysis showed a normal structure of the anterior and posterior lobes except for a mild mononuclear infiltration at the margin of the pars nervosa. The microscopic diagnosis was extensive cortical encephalomalacia.

CASE 3: T. J., a 7 year old white male, was never seen by the author but was admitted to Baylor University Hospital at 4:40 p. m. on Sept. 27, 1945, on the service of Dr. W. H. Potts, through whose courtesy the case is being presented. The patient had been a known diabetic since January, 1943, and had last been seen by Dr. Potts in July, 1945. The patient had been on a diet consisting of 60 gm. protein, 120 gm. carbohydrate, and 75 gm. fat daily and had been taking 12 units regular insulin and 10 units protamine zinc insulin daily. He apparently had been getting along satisfactorily on this program except for occasional morning insulin reactions for several weeks prior to his present hospital admission. These were usually satisfactorily relieved by orange juice. On the morning of Sept. 27th when the mother tried to awaken the patient, he had a slight convulsion. He was given orange juice and was later given his usual daily insulin. He ate very little breakfast

and fell to the floor before finishing the meal. As his home was in a town quite some distance from Dallas, the patient was seen by a local doctor, was given another 10 units of regular insulin, and was given more fruit juices and milk. However, the patient vomited what little food he took. Attempts to correct the patient's difficulty by giving glucose intravenously and syrup rectally were apparently unsuccessful. As the patient continued to have convulsions and was comatose it was decided to bring the child to Dallas, the patient being admitted to the hospital upon his arrival.

Upon admission the patient was comatose but the skin was dry. He occasionally groaned and appeared restless. He voided involuntarily. At times he had spastic types of convulsions in the opisthotonus position and had clonic rhythmic contractions of both arms in the flexed positions. The eyes became set to the right, and the pupils were dilated. Respirations were shallow and irregular; mucus appeared to have accumulated in the chest and rales and rhonchi were heard over both lung fields; the patient became cyanotic and at intervals had to be given artificial respiration because of apnea. Temperature was 104.0° rectally; pulse, 130; respirations, 30; and blood pressure 130/80.

Emergency blood sugar level upon admission was 56 mg. per 100 cc. and blood CO₂ combining power was 56 vol. %. The patient was given 70 cc. of 50% glucose and 1000 cc. 5% glucose intravenously. Blood sugar determination at 6:30 p. m. was 421 mg. At 12 midnight the blood sugar level was 222 mg. The patient showed no improvement. He was given 10 units regular insulin at 12:40 a. m. on Sept. 28th. His clinical course continued unchanged. The 8 a. m. blood sugar level on Sept. 28 was 80 mg. and blood CO₂ combining power was 54 vol. %. Lumbar puncture at 8 p. m. on Sept. 27th revealed clear colorless fluid with a pressure of 8 mm. mercury, rising to 20 mm. upon Queckenstedt's test, and then dropping to 10 mm. mercury. The fluid contained 3 white blood cells and 74 red blood cells per c.mm. of fluid. The globulin content was 10 mg. White blood cell count on admission was 7,700 with 1% young, 19% band, and 66% segmented polymorphonuclear cells, and 14% lymphocytes. Hemoglobin was 9.8 gm. and red cell count 3,350,000.

Because of the pulmonary edema and

fever, the patient was given penicillin, 20,000 units intramuscularly every 3 hours. He was also placed in an oxygen tent, receiving 7 liters oxygen per minute. Mucus was aspirated from the trachea at intervals. At 9:00 a. m. on Sept. 28th the patient was given 10 units of regular insulin and 500 cc. of 5% glucose intravenously. He received another 500 cc. of 5% glucose intravenously at 2:30 p. m. His condition continued unchanged, there being occasional muscular twitchings and convulsions, with respirations ceasing at irregular intervals. At 6 p. m. on Sept. 28th, respirations ceased permanently.

Postmortem examination was performed by Drs. Howard J. Scott and Charles F. Pelphrey. No gross external abnormality was noted. The lungs were crepitant throughout, pale pink in color anteriorly and slightly dark red posteriorly. Multiple sections revealed a homogeneous appearance with pink watery fluid exuding from the cut surfaces of both lungs. Occasional areas showed slight mottling, however, not interpreted grossly as bronchopneumonia. The heart was grossly normal. There was some passive hyperemia of the spleen and fatty degeneration of the liver. Passive hyperemia and cloudy swelling were found in the kidneys. Pancreas, adrenals, and other abdominal viscera were normal in appearance. Examination of the brain showed cerebral edema and scattered numerous small dark red spots which did not rub off easily, suggestive of petechial hemorrhages.

Microscopically there were multiple recent capillary hemorrhages in the heart; hypostatic edema, marked hyperemia, and early hypostatic pneumonia with recent small hemorrhages in the same area of lungs; hyperemia and acute parenchymatous degeneration of the kidneys; no evidence of substantial glycogen storage in the liver; hyperplasia of the malpighian corpuscles of the spleen; islets of Langerhans small with cells having a scanty amount of cytoplasm; hyperemia and hyperplasia of the medulla of the adrenals; and marked, hyperemia, lymphocytic hyperplasia, and acute lymphadenitis of the mesenteric lymph nodes.

A less extensive study of the brain was made than that reported in Case 2. However, later study of the sections available, as reported by Dr. Paul M. Levin, revealed moderate to marked hyperemia and slight edema in some areas of the cortex and prob-

able diffuse loss of ganglion cells from the second and third layers of cerebral cortex.

Comment. Dameshek, *et al.*,¹⁰ have shown that the difference in dextrose content between blood drawn from the carotid artery and the internal jugular vein was greater than that between the brachial artery and the basilar vein, and Himwich²⁰ has shown that oxygen utilization and the metabolic rate of the brain are decreased during severe hypoglycemia. Gerard¹⁶ reported that the respiration of the brain, that is, oxygen consumption per unit mass, is about thirty times as intense as that of muscle or nerve. It is generally agreed that dextrose is essential in normal utilization of oxygen by brain tissue and that acute anoxia or hypoglycemia affects first the cerebral cortex, next the upper portion of the brain stem, and finally the medulla.^{15,16,20,20a,21,29,31,44}

Grayzel¹⁹ reported that rabbits in which hypoglycemia was experimentally produced showed definite central nervous system lesions and that zones of necrobiosis were more noticeable in the pyramidal cells of the third and fifth cortical layers.

Other animal experimentation has shown hypoglycemia to produce liquefaction, vacuolization and homogenization of ganglion cells, marked shrinkage of cytoplasm and nuclei, diminution in number of neurons in various cortical areas, and small microscopic hemorrhages.^{7,41,45} Sherrill and Mae Kay⁴² reported a variable degree of hemorrhagic edema of the lungs in experimental animals with hypoglycemia, probably similar to the pulmonary edema seen in Case 2 when the patient was first seen in hypoglycemia and similar to the pulmonary edema seen in Case 3. Baker^{3,4,5,27} at first believed that changes found in ganglion cells on postmortem examination of 3 patients dying after hypoglycemia were due to postmortem degeneration but in later papers concluded that these were antemortem changes. He subsequently reported extensive brain damage, congestion, hemorrhages, patchy demyelination, cyst formation, encephalomalacia with necrotic and active prolifer-

ation, various degrees of cellular degeneration, and gliosis following hypoglycemia. Numerous other similar reports have now appeared.^{23,25,26,35,38,40,45} "It is indeed difficult to distinguish less severe nerve-cell changes from postmortem alterations."²⁶

Schereschewsky and others have reported necrosis and hemorrhage into the adrenal glands after hypoglycemia.^{25,36,41} Perhaps the adrenal gland changes reported in Case 2 were antemortem changes rather than postmortem degeneration. If so, this could account for the patient's decreased insulin requirement after his hypoglycemia although he continued to receive 350 gm. carbohydrate daily.

Clinically, cases of posthypoglycemic encephalopathy have been reported in every age group, as frequently in children as in adults. Raseoff *et al.*³⁶ reported a case of hypoglycemia of the newborn with hypertrophy and hyperplasia of the islands of Langerhans, dying 13 hours after birth from a latent diabetic mother. Although posthypoglycemic encephalopathy, to the author's knowledge, has not definitely been reported following hypoglycemia of the newborn, it remains a definite possibility to be considered in determining the etiology of mental deficiency states of childhood. Darrow¹¹ had 2 cases of convulsions and mental deficiency in children following hypoglycemia. A case of transitory hemiplegia associated with hypoglycemia in a diabetic child with congenital heart disease was reported by Fischer.¹⁴ Allan and Crommelin¹ reported the case of a 6 year old diabetic with an insulin reaction in which the patient was stuporous for 3 days, followed by hemiplegia, aphasia, and epileptic seizures for 15 months. In Wilder's case⁴⁸ an 8-year old child had idiocy secondary to a degenerative lesion of the brain from overdosage of insulin. Unconsciousness persisted for 6 weeks, and the mental condition never returned to normal. Anderson² had a 7-year old diabetic patient with a severe behavior disorder following hypoglycemia and a 13-year old diabetic with an insulin reaction followed by 4 days of coma and then gross dementia

which gradually but only partially improved during the next 15 months. Fenz and Kogerer¹³ reported the case of a 16-year old boy in which a severe insulin reaction was followed for a fortnight by a syndrome characterized by negativism, cataplexy, grimacing, and motor restlessness, with subsequent improvement but persistence of apathy and dulness after 4 months. Terplan's case⁴³ has already been mentioned.

Numerous similar cases have been reported in adults, not only in diabetics,^{8,14,46} but also following the Sakel form of shock therapy for schizophrenia,^{12,17,34,39} and in cases with pancreatic adenoma.^{6,23,30} The case reported by Root and Styron²⁸ in which the patient remained in a comatose state for 23 days and finally died with terminal bronchopneumonia and sepsis is similar to Case 2. Another similar case with coma for 17 days terminating in death is reported by Lawrence *et al.*²⁶ Cases with Korsakoff's syndrome persisting for several months after hypoglycemic shock have been seen.^{24,33} Also found are cases in which a combination of hypoglycemia and arteriosclerosis seemed to cause the cerebral damage.²⁵ Murphy and Purtell³⁵ reviewed 26 cases of hypoglycemia with cerebral damage and concluded that the most common aftermath was profound mental and personality damage, extensive damage leaving the patient with the intellectual level of idiosy, less damage resulting in mental retardation, apathy, and dulness, at times progressing to true psychoses. Parkinsonism, aphasias, hemiplegias, and objective neurologic changes have persisted for months.

Goldman concluded: "Coma persisting after cessation of hypoglycemia is an entity in itself and related only in a secondary sense to the hypoglycemia."¹⁵ Thus, in Case 1 a state of mental confusion and change in personality, apparent clinical persistence of hypoglycemia, remained for 3 days after he was first seen and for 48 hours with high blood sugar levels after the 3:30 p. m. blood was reported as showing no trace of glucose the day after admission to the hospital. This drop in

blood sugar level under these circumstances was undoubtedly the result of loss of liver glucose by glycogenolysis during the severe insulin reaction on the preceding day and indicates the high degree of sensitivity of an individual to insulin after a severe hypoglycemic episode and the necessity of continuing high carbohydrate intake in spite of high blood sugar levels in such cases. The clinical picture was not due to persistent hypoglycemia but to transient cerebral damage caused by the preceding hypoglycemia. In Case 2, apparent idiosy, aphasia, and neurologic changes remained for 18 days after the blood sugar returned to normal or high levels. Case 3 died after having remained comatose with occasional muscular twitchings, convulsions, and irregular respirations for 24 hours after termination of hypoglycemia. The term, posthypoglycemic encephalopathy, although to the author's knowledge not previously used in the literature, seems to be the preferable descriptive term for this clinical entity.

Conclusions. Numerous cases of personality, mental, and neurologic changes following hypoglycemia and persisting after the blood sugar levels have become normal have been previously reported.

The physiological and pathological changes responsible for the clinical behavior are briefly discussed.

Three cases belonging in this clinical group are reported, one with mental confusion and personality changes for 48 hours after cessation of hypoglycemia; one with marked mental impairment and persistent neurologic finding for 18 days, terminating in death; and a third terminating fatally with coma and convulsions for 24 hours after the hypoglycemia was satisfactorily controlled. Postmortem findings in the last 2 cases are reported.

It is recommended that the term posthypoglycemic encephalopathy be used for this very definite clinical entity.

Members of the medical profession should be aware of this very serious complication of hypoglycemia and combat any prolonged low blood sugar level vigorously.

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PLASMA PROTEINS

II. ALTERATION IN ALLOXAN DIABETIC RABBITS ESPECIALLY IN RELATION TO OCULAR DAMAGE

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In previous studies changes in the plasma protein distribution in clinical diabetes mellitus as measured by the Tiselius electrophoresis method were reported.⁵ Reduction in total albumin and elevation of the β -globulin fraction were demonstrated in uncontrolled diabetes. With adequate treatment, a return to normal occurred. It was also suggested that cases complicated by diabetic retinitis showed a still greater deviation from normal and distinctly less improvement with diabetic control.

Alloxan administered in appropriate amounts results in the production of permanent islet cell damage in rabbits, rats and dogs.^{2,3,4} In this study on alloxan diabetic rabbits we wished, first, to determine what modification, if any, occurred in plasma protein fractions, and, second, to note the progress of these changes with different combinations of insulin, diet and vitamins. During the course of the studies the eyes were examined for lens and retinal changes.

Animals. In early studies 7 albino rabbits, 4 Belgian hares, and 5 others of a mixed strain were used. Later studies were made on Belgian hares, because of the more even distribution of retinal pigment. In the albino visualization of fundus vessels is more difficult.

Twenty-four rabbits were used. Alloxan, 100 mg. per kg. body weight, was administered intravenously to 20; 2 were kept as normal controls. Two rabbits received repeated small injections. Three animals were bled repeatedly prior to administering al-

loxan in order to lower plasma albumin levels and to witness the effects of this upon susceptibility to later retinal hemorrhage. If evidence of hypoglycemia was manifested at any time during the 24 hours after injection, 50% dextrose solution was given intravenously. The 2 normal control rabbits were treated identically insofar as bleeding, diet and examinations were concerned.

Methods. Blood glucose was determined by the Benedict blood sugar method before and after development of diabetes. Urinary glucose was determined qualitatively or quantitatively by the Benedict method. To determine the occurrence of chemical nephritis, the urine was examined for albumin and red cells.

The D/N ratio was determined on aliquot portions of a 24 hour urine specimen collected from the 48th to the 72nd hour of a 72 hour fast. Nitrogen was determined by the Pregl modification of the micro-Kjeldahl method.

The Tiselius electrophoretic technique was used for plasma protein fractionation.⁴ Blood was drawn from the femoral artery. Potassium oxalate was used as anticoagulant.

Diet. Diet 1 consists of oats *ad lib.* and approximately 4.5 ounces of carrots and 4 ounces of greens daily (celery greens, cabbage, lettuce or green hay). Approximately 2 ounces of oats daily were eaten by most of the rabbits.

Diet 2 consisted of Purina rabbit pellets *ad lib.* and either celery or lettuce greens. The average rabbit consumed 3 to 4 ounces of pellets a day, 4.5 ounces of carrots, and 4 ounces of greens.

Eye Examination. The eyes were examined after maximum dilatation of the pupils with 1% atropine sulfate solution. The day before the examination 2 drops were administered about 5 P.M. The next morning drops were given about 9 A.M. in preparation for a noon examination. If dilatation was not complete, 2 drops more were given 2 hours later. If more rapid dilatation was necessary 2 or 3 doses were administered at $\frac{1}{2}$ hour intervals. When capillary hemorrhages were observed, the examinations were always viewed by a second ophthalmologist. Rabbits with and without hemorrhages and with and without diabetes were presented at random to the examiner, who was thus entirely unbiased.

Results. As previously reported, increased blood sugar and glycosuria were observed within 48 hours after injection of alloxan (100 mg. per kg. or more) into normal rabbits. After the initial injection, 18 rabbits developed permanent hyperglycemia. In 1 it appeared only after a second injection. One rabbit failed to show more than temporary elevation in blood sugar even after the second administration; 1 failed to become hyperglycemic after 2 injections. In 2 rabbits diabetes was produced by giving repeated smaller amounts of alloxan. One received 6 injections of 20 mg. per kg., whereas the other received 5 injections of 40 mg. per kg. at intervals of 3 days.

Acetoneuria was observed in 6 animals from the 4th to 12th day following development of diabetes. In 5 cases it was controlled by protamine-zinc insulin. On withholding therapy, ketosis occurred in only 1 case. This animal required 5 units of protamine-zinc insulin daily for the 1st month to combat signs of diabetic acidosis. From the 2nd to 5th month inclusive, insulin in similar dosage 3 times a week prevented ketonuria. Therapy was then stopped, and the animal appeared in good condition until food was withheld for 72 hours in order to determine the D/N ratio. Severe acidosis resulted and death followed despite treatment with large amounts of insulin and intravenous fluids. The animal had moderately severe

diabetes as judged by the D/N ratio, 2. Some animals, however, had even higher ratios, but had less tendency to excessive ketone body production. All of the animals in this group were in about the same nutritional condition and received the same diet.

As was previously observed in untreated diabetic patients, rabbits with severe diabetes and acidosis usually showed a decrease in albumin, and a pronounced increase in the β -globulin fraction (Tables 2 and 3). When ketosis ceased and the animal's condition improved, either after treatment with insulin or after some spontaneous adjustment, the β -globulin returned to normal. In insulin-treated animals the albumin level frequently increased.

Rabbits with mild diabetes (Table 1, R-8) usually showed a decrease in total plasma protein and albumin but no significant modification in β -globulin. When insulin therapy reduced glycosuria to a trace to 1+, the total protein and albumin levels tended to return to normal.

Animals with moderately severe diabetes (Table 1) but without acidosis showed plasma protein shifts of a degree comparable to those observed in uncomplicated diabetes in man.

During the course of diabetes in the rabbit many animals showed eye changes. Modifications in the plasma protein picture were not necessary accompaniments of developing lens opacities. On the other hand, a low plasma albumin and an elevated β -globulin were nearly always found at the time that fine capillary bleeding in the retina was observed. The interval before appearance of eye changes varied greatly from animal to animal (Table 4) and seemed to have little correlation with the severity of the diabetes, loss of weight, or diet. One rabbit (D/N 0.7) showed lens vacuoles 6 weeks after, and fundus changes $4\frac{1}{2}$ months after islet cell damage was produced. In another animal with mild diabetes (D/N 0.5) 3 months elapsed before lens changes and $3\frac{1}{2}$ months before

capillary bleeding were noted. However, 1 animal (D/N 0.75) showed capillary hemorrhages 1 month and lens cloudiness 2 months after onset of diabetes.

Of the 21 diabetic rabbits, 18 showed progressive lens changes, apparently quite similar to those described by Bailey and Bailey.¹ Six rabbits were given large amounts of vitamins in addition to protamine-zinc insulin in an attempt to prevent or delay development of lens changes (Table 1). None of the group failed to show lens opacities. Because of the wide variation in the time required for these changes to occur in the untreated diabetic rabbit as well as in the treated animal, a much larger series will have to be studied

before any conclusions as to the effect of vitamin therapy can be drawn.

In 8, retinal changes, which in some instances persisted for 6 weeks, consisted of very fine, minute capillary bleeding along the larger vessels. It was possible to follow pigment deposition at the site of bleeding as the hemorrhages were absorbed. No exudates have been observed either clinically or on microscopic examination of the retina. Apart from minor retinal changes, none have been observed to compare with the severe retinal degeneration in diabetes mellitus in man.

Microscopic examination of the eyes of 4 of the rabbits was made. In Rabbits R-3, R-7 and R-17 (see illustration), the

TABLE 1.—PROTOCOL OF DIABETIC RABBIT 2
Brown and white. Alloxan injections 4/3/44 and 4/27/44.

	Mar.	April	May	June	July	Aug.	Sept.	Oct.	Mar. 1945
Fasting blood glucose, mg./100 ml.	75	250	350	350	
Urine:									
Glucose, gm./24 hr.	0	22	12	21	Trace	0 to trace		
Acetone	0	4+	0	2+	0	0		
Protamine-zinc insulin, U/24 hr.				6/26	8/26			
Vitamins*	9/14	3			
Lens changes OD	Clear	..	Diffuse central opacities	Progressing	Early post-central	Central remain same	Much more definite central and periphery		Definite, especially central; extreme clouding of lens
OS	Clear	..	OS OD	Progressing		Central remain same	Much more definite central and periphery		
Retina	Normal	Occasional vacuoles in periphery	Not clearly seen		
Total plasma protein	3/30	4/20	5/16					10/2	
Gm./100 ml.	5.18	4.99	4.81					5.87	5.86
Albumin:									
Gm./100 ml.	3.20	3.19	3.05					3.41	3.62
%	61.80	63.80	63.10					59.10	61.90
α -Globulin:									
Gm./100 ml.	0.17	0.27	0.20					0.40	0.15
%	3.20	5.40	4.10					7.20	2.70
β -Globulin:									
Gm./100 ml.	0.92	0.74	0.72					0.89	0.70
%	17.80	14.90	14.90					15.40	11.90
γ -Globulin:									
Gm./100 ml.	0.52	0.40	0.54					0.77	0.78
%	10.00	8.00	11.10					15.40	13.20
Fibrinogen:									
Gm./100 ml.	0.37	0.33	0.33					0.51	0.61
%	7.20	7.80	6.80					8.80	10.40

* Daily dose.

Vitamin A, 10,000 U.
Thiamine chloride, 3 r.
Riboflavin, 6 mg.
Pyridoxine hydrochloride, 1.5 r.
Nicotinic acid, 30 mg.

Calcium phosphate, 10 r.
Dose stated fractionally—total amount concentrated in 10 equal portions
0.6 gm.
Ascorbic acid, 50 mg.
Liver extract (L. 1) 1 cc

TABLE 2.—PROTOCOL OF RABBIT 3
♀ Albino. Alloxan injection 4/3/45 and 4/13/45.

	March	April	May	June	July	August	September	October	November	January
Fasting blood glucose, mg./100 ml.	72	..	5/8 320	..	100	..	9/6 120	10/10* 225	..	315
Urine glucose, gm./24 hr.	0	..	31	..	3	21
Acetone	4+
Protamine-zinc insulin, U/24 hr.	0	6/26	3	8/24	..	4	11/17	0
Lens changes: OD	Clear	Clear	Clear	Fine postcentral lens changes	More marked postcentral and early periphery lens changes	..	More marked	Lens changes extensive
OS	Clear	Clouding	Central lens changes three dots	Same	9/27 same	..	More marked	Lens change—more extensive than OD
Retina	5/9 two fine capillary hemorrhages in fundus OD	6/23 new hemorrhage OD	..	8/7 no new hemorrhage	9/27 fine hemorrhage anterior OS	..	11/17 not clearly visualized	1/16 not visible
			5/23 4.97		..					
Total plasma protein: Serum	5/8	5/8		4.86		5.22	5.42	..	5.79	5.47
Albumin:										
Gm./100 ml.	2.50	2.50	2.80	2.13	..	3.20	3.46	..	3.44	3.25
%	35.90	35.90	56.20	43.90	..	61.20	60.30	..	59.40	59.40
α-Globulin:										
Gm./100 ml.	0.47	0.47	0.40	0.42	..	0.36	0.40	..	0.48	0.29
%	10.60	10.60	8.10	8.60	..	6.90	7.40	..	8.30	5.30
β-Globulin:										
Gm./100 ml.	0.86	0.86	0.89	0.78	..	0.49	0.61	..	0.68	0.66
%	19.30	19.30	18.00	16.00	..	9.40	11.20	..	11.80	12.10
γ-Globulin:										
Gm./100 ml.	0.37	0.37	0.52	0.85	..	0.53	0.60	..	0.72	0.79
%	8.10	8.10	10.40	17.40	..	10.20	11.00	..	12.40	14.50
Fibrinogen:										
Gm./100 ml.	0.27	0.27	0.36	0.68	..	0.64	0.55	..	0.47	0.48
%	6.10	6.10	7.30	14.10	..	12.30	10.10	..	8.10	8.70

Conclusions: 1. Before insulin: total fell; albumin fell appreciably; 2 hemorrhages occurred; some rise in all globulin fractions
2. After insulin: total rose and approached normal; albumin tended to rise; globulin fractions tended to fall, none reaching normal, however.

* Acute upper respiratory tract infection.

abnormal changes were all of similar nature, but varied in degree. In the sections of the eyeballs, in the posterior part of the retina, on both sides of the entrance of the optic nerve, for a considerable distance, there were some small circular, irregular or elliptical disk-like foci of amorphous granular, deeply eosinophilic material, situated beneath the inner limiting membrane and partly occupying or

were present just beneath the inner limiting membrane. No obvious degenerative or inflammatory disease of the arterioles was detectable, so that the disks of eosinophilic material, if they did represent old hemorrhage, must have been of capillary origin. The fact that the blood elements were unrecognizable would indicate that these small foci of hemorrhage were not recent. The only other pathologic change

TABLE 3.—PROTOCOL OF RABBIT 24

B. H. Alloxan 100 mg./kg. injection 8/25/44.

	August	September	October	November	January
Fasting blood glucose, mg./100 ml. . . .	78	450	290
Urine:					
Glucose, gm./24 hr. . . .	0	36			31
Acetone	0	2+	0
D/N ratio	0.91
Lens changes:					
OD	Normal	Lens spot at 6 o'clock	Early peripheral	More marked peripheral diffuse central	Diffuse so dense retina could not be seen
OS	Normal	Early peripheral	More marked peripheral diffuse central	
Retina	Normal	6 fine capillary hemorrhagic areas along posterior vessels	Hemorrhage in both eyes numerous	Hemorrhage still present	
		OD OS normal			
Total plasma protein Gm /100 ml. . . .	Serum 4.74	9/12/44 4.59			
Albumin:					
Gm./100 ml. . . .	3.38	2.26			
%	71.20	49.20			
α Globulin:					
Gm./100 ml. . . .	0.20	6.30			
%	4.20	6.50			
β -Globulin:					
Gm /100 ml. . . .	0.36	1.24			
%	11.90	27.00			
γ -Globulin:					
Gm /100 ml. . . .	0.60	0.40			
%	12.70	8.70			
Fibrinogen:					
Gm /100 ml.	0.39			
%	8.60			

Diet: oats, carrots and greens

NOTE.—Severe diabetes in an untreated female rabbit showing very marked shifts in total albumin and β -globulin fractions. Changes may have been intensified and hastened by repeated plasmapheresis prior to administration of alloxan.

Bled 20 ml. 8/22, 23 and 24. Cells returned

compressing the ganglion layer. Within these foci there were some pale, minute golden brown pigment granules of variable size. Similar pigment granules were also present in the ganglion layer in this region. The disk-like eosinophilic foci suggested agglomerated, disintegrated red blood corpuscles but definite corpuscles could not be identified. In the ganglion layer, especially in the region of the eosinophilic disks, there were a moderate number of dilated capillaries filled with red blood corpuscles and some of these capillaries

in these eyeballs was lenticular cataract, which was most marked in the eyes of R-7 and only beginning in R-3 and R-17.

R-31 did not show the changes in the retina described above. The only change observed was vacuolization in the optic nerve. The nature and significance of this was not determined.

It may be noted that fundus examination of R-3, R-7 and R-17 had shown considerably more extensive capillary hemorrhages than were observed in R-31.

Where plasma proteins were experimen-

TABLE 4.—RELATION OF SEVERITY AND DURATION OF ALLOXAN DIABETES TO DEVELOPMENT OF EYE CHANGES IN RABBITS

Rabbit and breed	Blood glucose (mg./100 ml.)	Severity of diabetes			Duration of diabetes at onset	
		Urine		D/N	Lens changes (wks)	Capillary hemorrhages (wks)
		Glucose (gm./24 hr.)	Acetone			
2M	340	22	2+ for 2 wks after initial diabetes; none later	.	3	
3A	340	31	4+ for 4 wks.; 0 to trace afterward; 21st wk. 2+	..	8	5
5A	350	17	4+ to trace for 3 wks.	..	5	
7A	235	17	0	0.79	5	17
8A	200	12	0	0.50	Occasional vacuoles	
13BH	325	20	1+ for 1 wk.	.	12	14
14B	255	13	0	..	2	
15G	190	Trace	0	..	4	
17BH	280	20	0	..	16	
18A	254	22	0	0.70	3	14
23A	400	24	0	1.00	8	10
24BH*	450	36	1 to 2+ 2nd and 3rd wk.	0.91	2	
25BH*	300	23	Trace 1st wk.	1.75	3	1
27BH*		23	0	.	..	Aneurysmal dilatation of 1 venule
28BH†		31	4+ 1st wk.	2.00	6	
					Corneal serr and haziness	
					15	
					Lens opacities both eyes	
31BH†		10	0	0.75	6	3
32BH†		35	0	2.35	5	
35BH		32	0	3.58	5	
36BH		28	4+ 1st week	.	3	
40BH		25	.	0.75	3	
1BH normal control		0	0	0	1 large vacuole	
33BH† normal control		0	0	0	Normal for 26 wks observed	
29BH†	90	0	0	0	Normal for 12 wks. observed	
					Normal for 24 wks. observed	

* Repeatedly bled before alloxan Diet: oats unless marked † indicating Purina diet.

† Apparently resistant to alloxan. No diabetes, after 2 intravenous injections of 100 mg. per kg.

A, albino; B, brown; M, mixed; GR, gray; BH, Belgian hare.

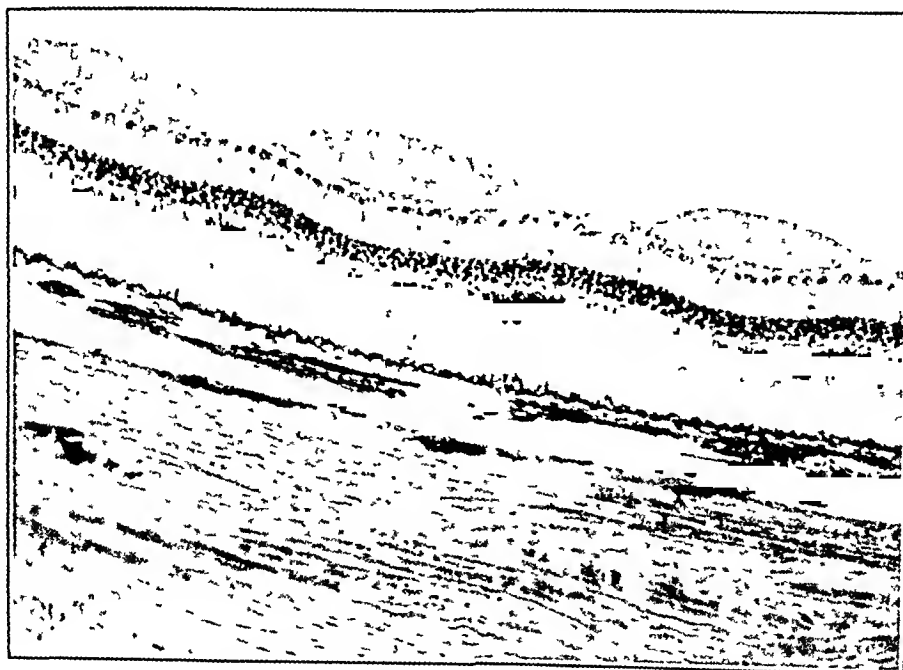


FIG. 1.—Typical changes observed in the right retina of R-17

tally depleted by plasmapheresis before the production of diabetes, retinal changes developed more rapidly. The fundi were examined after plasmapheresis and prior to alloxan administration to be sure that depletion of plasma proteins alone was not responsible for capillary bleeding.

The toxic effect of alloxan was probably not responsible for the capillary bleeding, for in some cases it was first observed 3 to 4 months after administration of the drug.

In 2 normal rabbits and the 1 which failed to become diabetic after 2 injections of alloxan, the eyes were normal on all examinations. These rabbits received the same diets as the diabetic animals. They were bled and the retinae examined at the same intervals.

Summary. Plasma protein fractionations (Tiselius technique) were made on 24 rabbits before and after the development of alloxan diabetes. In severe diabetes with acidosis there was a marked increase in the β -globulin and a decrease in the albumin level. With disappearance of acidosis, either following insulin treatment or spontaneous adjustment, the

β -globulin level became normal. In some cases with insulin therapy, the albumin approached the normal value.

In mild diabetes, without acidosis, there was frequently a decrease in the total plasma protein, but little change in the relative percentage of the various fractions.

Twenty-one of the rabbits showed progressive lens changes and 8 showed minute capillary bleeding in the retina. The plasma albumin was usually markedly decreased and the β -globulin increased at the time that hemorrhages were observed.

The rabbit which failed to develop diabetes following injection of alloxan also failed to show any plasma protein changes or eye abnormality.

Conclusions. Plasma protein changes which occur in the rabbit with alloxan diabetes (*i. e.*, a marked increase in the β -globulin and decrease in albumin levels) are similar to those which are observed in human diabetes. The development of ocular complications in rabbits demonstrates a further similarity between diabetes mellitus in man and diabetes produced by alloxan.

We wish to express our sincere appreciation to: Dr. F. B. Peck of the Lilly Research Laboratories for generous supplies of vitamins and insulin; Dr. J. Murray Scott of Ayerst McKenna & Harrison, and Dr. Merton C. Lockhart of the Lederle Laboratories, Inc., for vitamins. Mr. James Clark gave valuable technical assistance throughout the course of the experiments. We are indebted to Dr. A. D. Ruedemann, Dr. E. Perry McCullagh and Dr. Irvine H. Page for aid and suggestions during the course of this work. We wish to thank Dr. Harry Goldblatt for the histologic examination of the rabbit eyes.

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A ROUTINE METHOD FOR THE RAPID DETERMINATION OF SUSCEPTIBILITY TO PENICILLIN AND OTHER ANTIBIOTICS

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It is reasonable to assume that a variety of antibiotic agents will be available to the physician in the near future. Already penicillin and tyrothricin are available for the treatment of many infections caused by gram positive organisms. Although still in the experimental stage, streptomycin shows promise in combating diseases due to gram negative bacilli. No doubt other antibiotics will be developed with more or less specific activity for certain types of bacteria.

When several antibiotic agents are available, the clinician will be faced with the problem of selecting the correct one. Among the factors which will influence his decision, the most important is the relative susceptibility of the infecting organism. For example, *H. influenzae* is moderately resistant to penicillin⁷ but highly susceptible to streptomycin; pneumococci are penicillin susceptible but many strains are quite resistant to streptomycin. Neter¹³ studied the relative susceptibility of staphylococci to penicillin, tyrothricin and streptothricin and found a variety of susceptibility patterns. Resistance to 1 of the antibiotic agents does not appear to be related to resistance to the other 2. Strains of the same species not only display variation in relative susceptibility to 2 different antibiotics but they also show marked differences in their susceptibility to a single antibiotic.⁵ For example, Bondi and Dietz¹ found 13.9% of 116 freshly isolated staphylococci to be resistant to penicillin. Buggs and his associates³ have likewise shown that there is

great variation in the susceptibility of strains of the same species to streptomycin.

In view of the increasing number of available antibiotics, it is apparent that adequate bacteriologic study of infectious diseases should include routine tests for susceptibility. Several methods^{10,14} are available for determining susceptibility to penicillin. These procedures, however, require first the isolation of the organism in pure culture and on the following day the determination of susceptibility. Although the results are reasonably accurate, a delay of 2 days from receipt of the specimen is inescapable. Furthermore, in the instance of a mixed infection separate determinations must be carried out for each organism. A simple and more rapid test would be desirable even at the sacrifice of some degree of accuracy. Such a test is described in this paper.

The procedure to be reported is a modification of that described by Vincent and Vincent¹⁵ for the assay of penicillin. By placing filter paper disks saturated with antibiotic solution on the surface of a blood agar plate immediately after inoculation with a clinical specimen, it is possible to test susceptibility at the same time the primary culture is made. Following overnight incubation susceptibility of the organisms is determined by measurement of zones of growth inhibition surrounding the disks. Thus, an evaluation of susceptibility can be obtained within 24 hours, regardless of whether the culture contains 1 or several types of bacteria. Furthermore, as many as 3 different anti-

biotics may be compared simultaneously, although to date the authors' experience is limited to the use of penicillin and streptomycin.

Method. In this laboratory each specimen is streaked in an identical manner on 2 blood agar plates, 1 each for aerobic and anaerobic

incubation. The medium is a veal infusion agar prepared according to the method of Wright¹⁶ to which is added 2% tryptose and 10% defibrinated horse blood. The swab or loopful of fluid is drawn once across one side of the agar surface. This primary inoculum is restreaked with a sterile inoculating loop and is spread with parallel streak

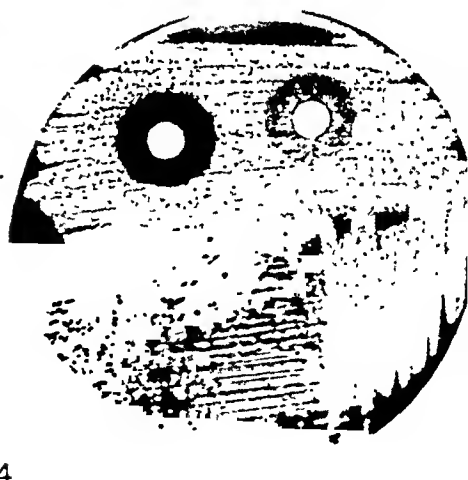
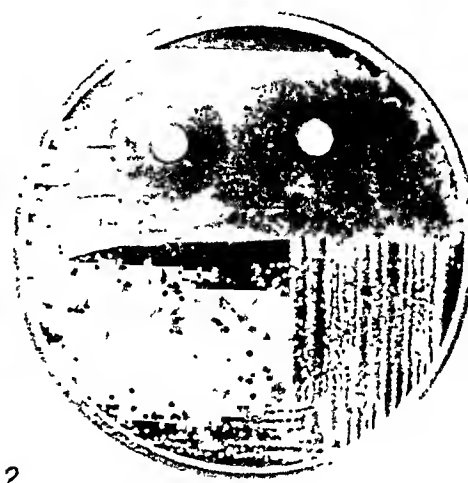
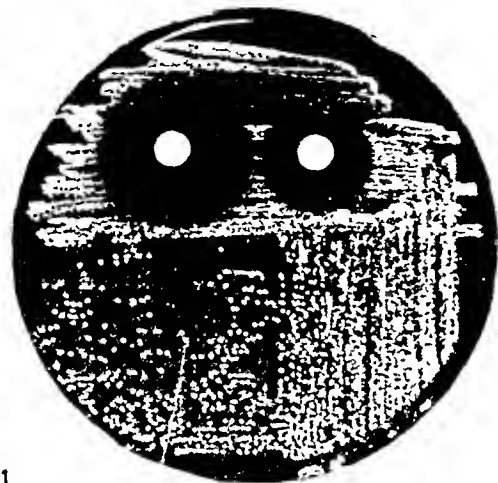


FIG. 1.—Disk susceptibility tests: veal infusion agar with 2% tryptose containing 10% defibrinated horse blood. In each figure disk on left side of plate is saturated with penicillin (15 units/ml.), disk on right saturated with streptomycin (500 μ g./ml.). 1, *Staph. aureus*; very susceptible (26 mm.) to penicillin; very susceptible (19 mm.) to streptomycin. 2, Hemolytic streptococcus; very susceptible (21 mm.) to penicillin; resistant (9 mm.) to streptomycin. 3, *Staph. aureus*; resistant to penicillin; very susceptible (19 mm.) to streptomycin. 4, *Heterococcus*; moderately susceptible (17 mm.) to penicillin (small inner zone); resistant to streptomycin. Hemolytic streptococcus; very susceptible (27 mm.) to penicillin (large outer zone); very susceptible (16 mm.) to streptomycin.

ing over one-third of the surface of the plate. After flaming the loop the plate is successively turned at right angles and streaked in the same manner, care being taken to touch the previous inoculum with each streak until the entire surface has been covered.

following preliminary trials with various strengths of each.

Following overnight incubation, both plates are examined for colony identification and for evaluation of the susceptibility of the predominant or pathogenic types present. Susceptibility is evidenced by the

TABLE 1.—RELATIVE SUSCEPTIBILITY BY THE DISK METHOD IN TERMS OF UNITS

Agent	Zone of inhibition; mm.	Susceptibility range	Relative susceptibility
Penicillin	>20	<0.1 units/ml.	Very
	10-20	0.1-0.4 units/ml.	Moderate
	<10	>0.4 units/ml.	Resistant
Streptomycin	>15	<4 μ g./ml.	Very
	10-15	4-15 μ g./ml.	Moderate
	<10	>15 μ g./ml.	Resistant

TABLE 2.—SUSCEPTIBILITY OF BACTERIA* BY DISK METHOD

Organism	No. strains	Penicillin			Streptomycin		
		Very	Mod.	Resist.	Very	Mod.	Resist.
β -Hemolytic streptococci .	17	15	2	0	1	2	14
Viridans streptococci	10	8	1	1	0	2	8
Non-hemolytic streptococci	9	5	0	4	1	2	6
Enterococci	4	2	1	1	0	0	4
Staphylococci .	8	6	0	2	7	1	0
Pneumococci	10	8	2	0	0	1	9
<i>E. coli</i> . . .	11	0	0	11	8	3	0
<i>A. aerogenes</i> .	2	0	0	2	2	0	0
Klebsiella .	1	0	0	1	1	0	0
Proteus .	2	0	0	2	2	0	0
<i>Ps. pyocyanea</i> .	6	0	0	6	0	2	4
<i>H. influenzae</i> . . .	16	0	1	15	11	5	0

* The significant organisms encountered in 54 selected clinical specimens.

Disks of Whatman No. 2 filter paper, 6.5 mm. in diameter, are cut with a cork borer or paper-punch; these are sterilized in a petri dish in the hot-air oven. By means of alcohol-flamed, fine-pointed forceps 1 of the disks is dipped into a solution of commercial penicillin carrying 15 units per ml. Excess solution is removed by placing the disk flat against the wall of the tube. A disk saturated in this fashion is placed gently on the surfaces of each of the inoculated plates in the area of the primary inoculum on the left side of the plate. In similar manner a disk saturated with a solution of streptomycin carrying 500 μ g. (500 *E. coli* units) per ml. is placed on the right side of the plate (Fig. 1). The disks should be at least 20 mm. apart and on a line parallel to the line of streak so that the inoculum around both disks is comparable. The recommended concentration of the solutions of penicillin and streptomycin were adopted

absence of growth around the disk, the larger the zone the greater the susceptibility. These zones are generally well defined and the diameter is readily measured with a millimeter ruler.

By comparing the size of the inhibition zone with the results obtained by streaking the same organism on the surface of agar containing known concentrations of antibiotic, it was possible to evaluate zone size in terms of units. It was convenient, furthermore, to employ the relative terms, "very susceptible," "moderately susceptible" and "resistant." The data on which these evaluations were made appear in Table 1.

Comment. The penicillin and streptomycin susceptibilities of the significant organisms encountered in 54 selected clinical specimens as determined by the disk method is presented in Table 2. In gen-

eral the results have been very satisfactory. The susceptibilities as determined by this method compare well with those obtained by more sensitive methods.^{3,11} It is not the intention of the authors, however, that this method should replace the more sensitive methods. It is designed as a routine test and as a guide in therapy. It may be carried out in any hospital laboratory. The rather broad limits of susceptibility by this method are believed to be sufficiently accurate for the purpose.

In determining criteria of susceptibility the authors were guided by blood level concentrations of both agents which are usually attained by recommended dosages.⁹ Concentrations of penicillin and streptomycin greater than 0.5 units and 25 μ g. per ml. of blood respectively are difficult to maintain for prolonged periods of time. It is not to be expected that infections caused by organisms with sensitivities of this magnitude or greater will respond to penicillin and streptomycin therapy.

Certain precautions are recommended in carrying out the test. Whereas the solution of streptomycin is quite stable and may be used for several weeks if stored in the refrigerator, the solution of penicillin should be prepared at least once a week and likewise stored in the refrigerator. Solutions of both agents in the concentrations recommended are best prepared in N/15 phosphate buffer, pH 6 for penicillin and pH 8 for streptomycin. Disks should be placed in comparable positions with respect to inoculum. The amount of growth naturally influences zone size, although slight variations in zone size do not materially affect final evaluation of relative susceptibility. Occasionally, heavy growth of a resistant organism may mask zones of inhibition of susceptible organisms. In such instances it may be necessary to subculture the latter organisms to fresh plates and repeat the tests. Inocula from specimens from the upper respiratory tract or from the intestinal tract where a large normal flora is generally present should be kept

to a minimum to prevent overgrowth by such resistant organisms.

Occasionally, one encounters within a zone of inhibition a colony or colonies of a susceptible organism. The authors have considered such colonies resistant variants. The production of these resistant forms by an organism which appears to be susceptible may be of great importance in view of the recent reports concerning the mechanism of development of resistance to penicillin⁴ and streptomycin.⁵ In evaluating the susceptibility of such a culture, the possibility of resistant variants being produced should be taken into account.

Streptomycin differs from penicillin in that it diffuses poorly and is adversely affected by certain ingredients in culture media.^{2,6} In an attempt to offset the smaller zones produced by streptomycin, a high concentration (500 μ g. per ml.) of that agent was employed. Moreover, since the activity of streptomycin is reduced under anaerobic conditions,^{2,6} zones of inhibition on anaerobic plates are either absent or smaller than those on the aerobic plates. It is recommended, therefore, that only the aerobic plate be used in evaluating susceptibility to this agent. This is not true of penicillin; the zones produced by this agent are similar on both plates.

This method may be used readily for testing susceptibility to any antibacterial agent which is water-soluble and diffusible in agar. Susceptibility to tyrothricin was attempted by this method but was unsuccessful because of its insolubility. Morley¹² recently described a test similar to that of the authors in which determinations of susceptibility to sulfathiazole as well as penicillin were attempted. As a whole the results with sulfathiazole were poor and did not appear to warrant use of this method for the routine testing of susceptibility to sulfonamides.

Aside from its value in determining susceptibility, the routine use of this test assists in colony identification. With a general knowledge of the relative suscep-

tibility of the important pathogens to penicillin and streptomycin, one is often guided by the zones of inhibition in identifying colonies of *H. influenzae* and other bacterial types.

Summary. A simple method is described for determining susceptibility to penicillin and other antibiotics at the time

of primary isolation. Its essential feature is the placing of filter paper disks saturated with antibiotic solution on the surface of a blood agar plate immediately after its inoculation with a clinical specimen. The routine use of this procedure provides valuable assistance in the selection of the proper antibiotic agent.

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THROMBOPHLEBITIS ON THE MEDICAL SERVICE OF A GENERAL HOSPITAL

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THE subject of thrombosis and embolism has received increased attention in the surgical literature during recent years. This has resulted from the recognition of the condition of quiet deep venous thrombosis originating in the foot and calf (the "bland thrombosis" of Homans and the "phlebothrombosis" of Ochsner) and the introduction of surgical treatment in the form of proximal ligation and thrombectomy.

The frequency of thrombophlebitis complicating medical illness is often not fully appreciated by the internist, and consequently this complication is all too frequently unrecognized during its early stages. Likewise, proper preventive measures are often neglected. Constant vigilance must be maintained to arrive at early diagnosis, upon which depends the prevention of pulmonary embolism and limitation of disability from residual venous obstruction. During the first 18 months of operation of this General Hospital on the Assam-Burma border, thrombophlebitis was rarely diagnosed on the Medical Service. In recent months the occurrence of pulmonary embolism in several patients with scrub typhus has directed our attention to the frequency and importance of deep venous thrombosis. During the past 4 months (Nov. '44 to Feb. '45), thrombophlebitis has been diagnosed 10 times in 9 patients. These cases have been analyzed and the problem of thrombophlebitis in general is discussed with reference to the more recent reports.

Material. There were 10 instances of thrombophlebitis occurring in 9 patients, all of whom were American soldiers. Eight of these developed in patients with scrub typhus during the management of

130 consecutive cases of this disease—an incidence of 5%. One developed in a patient suffering from a depressive psychosis and one in a patient with acute infectious arthritis.

All occurred in the lower extremity. There were 6 instances of primary involvement of calf veins, in 2 of which the process extended into the femoral veins (Cases 1 to 5). There were 2 instances in which the thrombophlebitis apparently originated in the pelvic (ilio-femoral) veins (Cases 8 & 9). In 2 patients the site of origin could not be accurately determined, since the process involved the whole venous system of the leg from calf to pelvis at the time of recognition (Cases 6 & 7). A brief summary of each case is given in Table I.

Diagnosis. The early recognition of thrombophlebitis complicating an illness depends upon the alertness of the physician and a knowledge of the early manifestations of such a lesion.

(1) *Thrombophlebitis limited to the calf veins.* Symptoms and signs were present quite early in our cases of deep calf vein thrombosis. In all 6 cases attention was directed to the lesion by the complaints of discomfort and stiffness in the affected calf. Such mild symptoms do not always evoke spontaneous complaint from a patient whose attention is centered upon other more distressing ailments. In two instances specific questioning was necessary to ascertain the presence of calf discomfort. Homans' sign (increased pain in the calf on passive dorsiflexion of the foot associated with tenderness to palpation) was present in all cases at the time symptoms were first noted. Appreciable swelling and vasomotor, color, and temper-

ature changes in the lower leg were absent as long as there was free flow of blood through the femoral vein. Fever, usually not exceeding 99.5° F., was present.

(2) *Thrombophlebitis limited to the calf and femoral veins.* Involvement of the femoral vein manifested itself by signs of (1) inflammation (pain and tenderness) along the course of that vessel and (2)

obstruction to venous return in the lower leg (superficial venous dilatation, warmth, cyanosis, and swelling below the knee). There was usually low-grade fever not exceeding 100.5° F. but the systemic reaction was mild. It should be emphasized here that these findings may be absent while a long propagating thrombus, attached only in the calf, floats free within

TABLE 1.

Pt. Primary disease and Site of 'phlebitis	Symptoms and signs	Treatment	Course and results
1. Scrub typhus. (a) R. calf veins. (b) L. calf and femoral veins.	(a) Calf pain, tenderness, and positive Homans' sign noted 14th day of illness. (b) Calf pain, tenderness, and positive Homans' sign; pain and tenderness over femoral vein; warmth, cyanosis, superficial venous dilatation, swelling of calf; leg held rigidly semi-flexed; fever 100°; noted 42nd day of illness.	(a) None. (b) Bandage, elevation and exercise. Ligation L. fem. vein, 43rd day. P-V injection 43rd, 44th, and 45th days.	(a) Therapy neglected due to failure to diagnose the lesion. No embolism. (b) P-V injection necessary for relief of pain following ligation. Ambulatory on 47th day. No embolism. Residual disability requiring disposition to U. S. A.
2. Scrub typhus. R. calf veins.	Calf pain, tenderness, and positive Homans' sign noted 15th day of illness.	Bandage, elevation, and exercise. P-V injections 15th, 16th and 18th days.	Good results. Ambulatory on the 16th day. No embolism. Returned to duty.
3. Scrub typhus. R. calf veins.	Calf pain, tenderness, and positive Homans' sign noted 22nd day of illness.	Bandage, elevation, and exercise. P-V injection 33rd day.	During 10 days of bandage, elevation, and exercise, there was neither extension or improvement. Excellent result following a single P-V injection. No embolism. Returned to duty.
4. Scrub typhus. R. calf and femoral veins.	Pain rt. calf on 16th day of illness, not mentioned until 19th day. Pain, tenderness, and positive Homans' sign with moderate swelling of the calf present on 19th day. No signs over femoral vein.	Bandage, elevation, and exercise. P-V injection 19th day. Femoral vein ligation 19th day.	Severe pulmonary embolism 8 hours after the P-V injection. Ligation following the embolism. Long illness with residual disability in right leg requiring disposition to U.S.A.
5. Acute arthritis, right ankle. R. calf veins.	Calf pain, tenderness, and positive Homans' sign noted 8th day of immobilization.	Bandage, elevation, and exercise. P-V injection 8th day immobilization.	Immediate relief of symptoms and signs. No embolism. Returned to duty after arthritis subsided.
6. Scrub typhus. L. ilio-femoral veins.	Unrecognized until patient had been ambulatory for 45 days. Then swelling and discomfort without signs of activity.	Bandage, elevation, and exercise. Continuous I-V. Heparin 11 days.	No embolism. Residual disability in left leg required disposition to U. S. A.
7. Psychosis. L. calf and ilio-femoral veins.	At least 2 episodes of pulmonary embolism before 'phlebitis' was diagnosed. Calf pain, tenderness, and positive Homans' sign; pain and tenderness over the femoral vein and in the groin; warmth, cyanosis, superficial swelling of the whole limb; decreased pulsation of femoral artery.	Bandage, elevation, and exercise. Continuous I-V. Heparin 11 days.	Prompt subsidence of fever, symptoms, and signs. No further embolism. Febrile reaction to heparin 11th day. Residual disability sufficient to require disposition to U. S. A., even had this not been necessary due to the psychosis.
8. Scrub typhus. (a) L. ilio-femoral veins. (b) L. calf veins.	(a) Unexplained recurrence of fever of 103° 25th day illness. Signs of moderately advanced ilio-femoral thrombophlebitis 32nd day. (b) Signs of acute calf vein thrombophlebitis 43rd day—3 days after heparin discontinued.	(a) Bandage, elevation and exercise. Continuous I-V heparin 6 days. (b) P-V injection.	(a) Prompt subsidence of fever, symptoms, and signs. Ambulatory on 4th day of heparin. No embolism. Disability sufficient for disposition to U. S. A. (b) Prompt and permanent relief of symptoms. No embolism.
9. Scrub typhus. L. ilio-femoral veins.	Unexplained recurrence of fever to 103° on 30th day of illness. Signs of moderately advanced ilio-femoral thrombophlebitis on 30th day. Calf signs absent.	Bandage, elevation, and exercise. Continuous I-V heparin 8 days.	Prompt subsidence of fever, symptoms, and signs. No embolism. Residual disability sufficient to require disposition to U. S. A.

the lumen of the femoral vein if the wall of that vein is not actually involved in the process.

(3) *Ilio-femoral thrombophlebitis*. Frank ilio-femoral thrombophlebitis gave signs of more severe inflammation and obstruction. Rather marked pain and tenderness were present in the lower abdomen and femoral triangle. Swelling of the whole extremity from groin to foot was present in addition to heat, cyanosis, and superficial venous dilatation. In the upper thigh, the sulcus medial to the femoral artery, occupied normally by a compressible vein, was obliterated and the femoral arterial pulsation was reduced. Fever was present, intermittent in character and often reaching 104° F.

Cases 8 and 9 were instructive. These two patients were afebrile, ambulatory and convalescing satisfactorily from scrub typhus when a secondary rise in temperature occurred. As no other cause for fever was found, they were carefully examined daily for signs of a suspected thrombophlebitis and none was found for several days. Then suddenly in both of these patients, the findings of a moderately advanced ilio-femoral thrombophlebitis appeared. Even then signs of calf vein involvement were absent.

Treatment. For therapeutic purposes, our patients were divided into 3 groups: (1) those with signs of calf vein involvement only, (2) those with signs of both calf and femoral vein involvement, and (3) those with frank ilio-femoral thrombophlebitis.

In the first group, treatment consisted primarily of lumbar paravertebral procaine injections. We believe that this method is safe if one can be sure that the lesion is early and that no thrombus is present in the femoral vein.

For the second group, we employed ligation of the femoral vein. Lumbar paravertebral procaine injections were used only for the relief of pain after ligation.

The third group was treated with heparin, this being the only anticoagulant

available to us. Heparin was administered by continuous intravenous drip at a rate sufficient to maintain the clotting time between 30 and 40 minutes. "Bicycle" bed exercises were instituted on the third day of heparinization and the patients were made to walk on the fourth day. The use of paravertebral procaine injection in a patient who is receiving anticoagulant is definitely contra-indicated because of the danger of retro-peritoneal hemorrhage from needle puncture of vein in the paraspinal region.

In all 3 groups elevation, compression bandage, bed exercises, and earliest possible mobilization were used routinely.

Results. (1) *Thrombophlebitis limited to the calf veins*. The results of procaine sympathetic block were satisfactory in 3 patients (Cases 2, 3, 5) with thrombophlebitis limited strictly to the calf. There was prompt symptomatic relief with no extension of the thrombosis after the first injection. A single injection was sufficient in 2 instances, whereas 3 injections at daily intervals were necessary in the other. There was no residual disability and all of these patients were returned to full military duty. The remaining instance of thrombosis limited to the calf veins was untreated because of failure to diagnose the lesion at an early stage.

(2) *Thrombophlebitis limited to the calf and femoral veins*. One patient (Case 4) with calf and femoral vein involvement received a paravertebral procaine injection. Eight hours later this patient suffered a severe pulmonary embolism and the femoral vein was ligated immediately thereafter. In retrospect, this appears to have been an error in judgment. Following the ligation in this case there was permanent relief of pain in the leg. In one other case of calf-femoral vein thrombophlebitis in which the femoral vein was ligated, pain from venous spasm persisted until relieved by lumbar sympathetic procaine block. Both of these patients had residual swelling and disability severe enough to require disposition to the zone of the interior.

(3) *Ilio-femoral thrombophlebitis*. Good results followed heparin therapy in 3 treated cases of ilio-femoral thrombophlebitis (Cases 7, 8, 9). The process quickly subsided and no embolism occurred. In one of these (Case 8), the administration of heparin was discontinued after 6 days. Three days later, signs of acute deep calf vein thrombophlebitis appeared. These signs subsided rapidly after one lumbar paravertebral injection of procaine. There was one febrile reaction apparently due to heparin. This patient experienced a chill followed by fever of 104° F. for which no other cause could be found. The fever disappeared within a few hours following the discontinuance of heparin. The remaining case of ilio-femoral thrombophlebitis (Case 6) was untreated since it was quiescent when discovered. All of these patients had rather marked residual disability necessitating evacuation to the zone of the interior.

Comment. Considerable advances have been made in recent in the understanding of the fundamental problems of thrombophlebitis. Recognition of the fact that the pelvic veins are not the usual primary site of thrombophlebitis is of major importance. While the majority of thrombotic processes originate in the foot and calf veins, the pelvic veins are occasionally the initiating site.¹⁸ Observation of cases 8 and 9 supports this view.

The term "phlebothrombosis" has become used to differentiate between supposedly non-inflammatory venous thrombosis and frankly inflammatory ilio-femoral thrombophlebitis or phlegmasia alba dolens. It may be that this concept is not strictly accurate. Except in cases of purely traumatic origin, it appears that all venous thrombosis is associated with inflammation of the vein wall, that associated with phlebothrombosis differing only in degree from that in ilio-femoral thrombophlebitis. Jensen¹⁶ has called attention to the presence of microscopic inflammatory changes in sections of femoral veins removed at operation from cases of so-called phlebothrombosis.

Many cases of pulmonary embolism occur before the site of the thrombus has been detected. Thrombosis originating in the calf with a long, unattached, non-obstructive, centrally propagating thrombus is responsible for the majority of these cases.¹⁴ With constant vigilance on the part of the physician, many of these instances of calf vein thrombosis may be detected in time to prevent pulmonary embolism. When the picture of ilio-femoral thrombophlebitis has become manifest, there is much less danger of embolism; then obstruction to the lumen is complete, the thrombus is firmly attached, and the likelihood of a detachable thrombus extending beyond the junction of the external and internal iliac veins or of the two common iliacs is not great.

There have been three major therapeutic approaches to the problem of thrombophlebitis: (a) anticoagulant therapy, (b) sympathetic block by use of lumbar paravertebral procaine injections, and (c) surgical treatment by ligation of the vein above the thrombus with or without thrombectomy.

Following its introduction in 1938 by Murray and Best,¹⁹ heparin has been rather widely used to increase the coagulation time of the blood. Its utility has however been somewhat limited by difficulty of constant intravenous administration and expense. More recently Loewe and Rosenblatt¹⁷ have reported the use of heparin-Pitkin menstruum subcutaneously. Subsequently Loewe, Rosenblatt, and Hirsch¹⁸ have reported good results in treatment of 125 cases of thrombophlebitis of various types with heparin-Pitkin menstruum. Bauer⁷ from Sweden has reported enthusiastically on the efficacy of heparin in preventing extension of thrombosis. During a 5 year period while intermittent intravenous heparinization was used, only 3 fatalities from embolism occurred in 209 cases of deep thrombosis, as compared with 47 embolic deaths in 264 cases of thrombosis before heparin therapy was used. One of his deaths occurred before heparin was administered. One occurred

from fresh thrombosis in the opposite leg after discontinuance of heparin, the patient having not been allowed out of bed. He calls attention to the importance of mobilizing patients before heparin is discontinued. Most of the heparin failures have resulted from allowing the patients to remain in bed after the anticoagulant was discontinued.

Because of the ease of oral administration, dicoumarol has become popular as a means of delaying blood clotting. However its use is limited by the necessity of having laboratory facilities available for the daily determination of blood prothrombin levels. Dicoumarol has been extensively used by Barker and his associates^{4,5,6} in both prophylaxis against and treatment of thrombo-embolism. In a group of 138 cases of postoperative thrombophlebitis treated with dicoumarol, they had no fatal embolism and only 4 patients developed subsequent episodes of thrombophlebitis.⁶ Yahr *et al.*²⁶ have also recently reported good results in 57 cases of thrombophlebitis of various types treated with dicoumarol.

The lumbar sympathetic block was introduced by Leriche¹⁶ and popularized in this country by Ochsner and DeBakey.^{20,12,22} Good results, both immediate and permanent, have been cited by these and other authors from the use of this procedure in various types of thrombophlebitis. However Ochsner²³ has recently advocated that use of this procedure be reserved primarily for relief of vasospasm associated with ilio-femoral thrombophlebitis.

Interruption of the venous channels as a means of treating thrombophlebitis was initiated by Homans in 1937.¹³ Since then the trend has been toward more frequent use of vein ligation and thrombectomy. There are many reports of good results following surgical treatment of this nature.^{1,2,3,8,10,12,14,15,23,24,25} It has become common practice to ligate both femoral veins in the attempt to prevent further embolism even though signs of thrombophlebitis may be limited to one leg. Homans¹⁴ has advocated the use of iliac

or vena caval ligation in cases of repeated embolism. Some have advocated the use of anticoagulants in conjunction with interruption of the venous channels and (or) thrombectomy.^{2,15,24}

Even so, it remains apparent that no one of the procedures at use at the present time is adequate for the management of all forms of venous thrombosis or for the prevention of embolism. Unexplained failures have been noted with dicoumarol⁹ and embolism has occurred following the use of heparin.^{4,15} We have had a case of embolism following the use of sympathetic block. Six per cent of patients who have had embolism prior to vein ligation have a repetition of embolism following this procedure.² Dennis¹¹ has reported a case of severe ischemia following femoral vein ligation. The patient almost lost his leg and was still unable to walk on it 6 months later. This author strikes a note of warning and conservatism regarding indiscriminate vein ligation. One has to admit, then, that we have no perfect method with which to combat thrombo-embolism at the present time.

It has seemed to us that the indications for the use of one or more of the major forms of therapy differ considerably depending upon such factors as the site of origin of the thrombotic process, its duration and extent, and whether or not embolism has already occurred. By using sympathetic procaine block therapy for the group with thrombophlebitis limited to the calf, we were able to return this group to full military duty. Had femoral vein ligation been employed, disability sufficient to prevent return to full duty would have resulted. The use of sympathetic block for this sort of case is said by many to be dangerous and we emphasize that one should be extremely careful to select for this procedure only patients in whom the process is known to be early and in whom there are no signs to indicate thrombosis above the knee. Barker *et al.*⁶ state that there is evidence that when thrombophlebitis is diagnosed clinically, the thrombus which is present will almost

certainly not detach and become an embolus. The use of sympathetic block would seem particularly suited to the patient who develops calf thrombophlebitis after he has become ambulatory. The danger of embolism should be small indeed and they are spared the "minimal" immediate disability and the undetermined amount of permanent disability resultant to femoral vein interruption. In the one case in which embolism followed sympathetic block, it is noteworthy that there was clinical evidence of extension of the thrombosis into the femoral vein at the time of the procedure. The danger of embolism is greatest when a propagating thrombus occupies the lumen of the femoral vein. In such instances, it appears safest in spite of the disability which results to remove the clot and ligate the vein, perhaps employing anticoagulants subsequently. In ilio-femoral thrombophlebitis, the danger of embolism is much less and surgical procedures necessarily much more radical. Ligation of the iliac vein or the vena cava is a major surgical procedure which becomes formidable in a patient who is already suffering from a serious disease. Here it would appear that anticoagulant therapy is most useful.

In view of the danger and disability resulting from venous thrombosis, prevention assumes a most important role. An understanding of the factors which contribute to intravascular clotting is essential to any program of prevention. The principal factors in the development of this condition are: (1) decreased rate of blood flow, (2) injury to the endothelium, (3) increased coagulability of the blood, (4) increased vasomotor tone, and (5) the "X" factor—presumed to be of toxic nature, liberated into the circulation as a result of disease, injury, or operation. Factors promoting venous stasis were present in all of the cases presented here. The typhus patients were prostrated and confined to bed. In addition their beds were fitted with Gatch frames which allowed marked flexion of the knees and thighs—thus favoring a certain degree of

venous obstruction both at the knee and groin. De Takats¹⁰ has called attention to the Fowler position as a factor in venous stagnation. The psychotic patient lay immobile for long periods of time. The patient with arthritis was treated by immobilization of the affected extremity. With regard to injury to the endothelium, rickettsial diseases in general are known to damage the capillaries and small blood vessels. However, we know of no specific observations concerning the condition of the endothelium of the veins of the legs in scrub typhus. We have no observations concerning an increase in the coagulability of the blood, the vasomotor tone, or the "X" factor in these patients.

Simple prophylactic measures which include (1) elevation of the foot of the bed, (2) early institution of bed exercises, and (3) avoidance of the unnecessary use of the Fowler position, immobilization, and poorly applied constricting bandages should appreciably lower the incidence of thrombophlebitis. In very ill patients, nursing care should include massage and passive motion of the lower extremities in addition to the usual backrubs. We believe that the institution of the Army reconditioning program for bed patients as well as for convalescent patients is extremely important in the prophylaxis of thrombophlebitis.

Summary. (1) Ten instances of thrombophlebitis in the lower extremity were observed on the Medical Service of this General Hospital during a four month period.

(2) Eight of these developed in patients with scrub typhus fever.

(3) Early diagnosis was not achieved until we began to look carefully for the early signs.

(4) In our opinion, treatment of thrombophlebitis should be individualized depending on the location and extent of the lesion.

(a) Thrombophlebitis confined to the calf veins was treated by lumbar paravertebral sympathetic block with uniformly good results. This procedure prob-

ably tends to prevent central propagation of the thrombus, embolism did not occur, and patients were spared the prolonged disability which follows femoral vein ligation. The use of heparin or dicoumarin in these cases might help prevent propagation of the thrombosis. However, its use is usually unnecessary. The concomitant use of anticoagulant and lumbar sympathetic block is prohibited by the danger of retro-peritoneal hemorrhage.

(b) Thrombophlebitis involving the calf and femoral veins was treated by proximal ligation. Sympathetic block was used only for relief of pain after ligation. In one case of calf vein thrombosis with extension into the femoral vein, paravertebral procaine block prior to femoral ligation was followed promptly by pulmonary embolism.

(c) Ilio-femoral thrombophlebitis was treated with heparin, high ligation being inadvisable in these ill patients. The results were satisfactory.

(5) This choice of therapeutic methods for the treatment of specific thrombotic lesions seems rational. It has been successful thus far in preventing embolism and in minimizing disability.

(6) In addition to these specific measures, all three groups of patients were treated with elevation of the extremity, compression bandage, bed exercises, and early mobilization.

(7) Our observations suggest that all cases of ilio-femoral thrombophlebitis do not necessarily result from extension of a calf vein thrombosis; such a process may originate occasionally in the ilio-femoral region.

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PLASMA SUBSTITUTES

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THE need for an effective colloidal infusion solution without serious side effects stimulated a renewed interest in substitutes for plasma in the early years of the recent war. Could either the duration of the war or the response of the American people to the plea for blood donations have been predicted accurately, the program of investigations into plasma substitutes might not have been so extensive. Had that been the case, we could not have gained the knowledge of the physiologic properties and the physicochemical characteristics of so many substances suggested as plasma substitutes in such a relatively short time.

There is as yet no acceptable substitute for blood if one is to consider its oxygen-carrying function. Plasma has been accepted through necessity as a "blood substitute." The introduction of such materials as peetin, isinglass, methyl cellulose, globin, bovine albumin and gelatin has been for trial as substitutes for plasma rather than for whole blood. It is recognized, however, that the infu-

sion of any colloidal solution which increases the blood volume, augments the cardiac output and is, therefore, a blood substitute in a limited sense.

Many though the functions of plasma may be, the greatest uses for plasma are in the treatment of peripheral vascular collapse and in the maintenance of protein nutrition by the intravenous route. Inasmuch as the recent need was for a colloid to be used in combating shock, the criteria for a plasma substitute became the criteria for an agent for the treatment of circulatory collapse.

The Criteria for an Agent for the Treatment of Shock. Certain minimal specifications for a plasma substitute could be inferred from the physicochemical properties of the serum proteins which are responsible for the colloidal functions of plasma. It does not follow, however, that the properties of a plasma substitute must be identical with those of the serum proteins. By reasoning thus, it becomes easy to think in terms of physicochemical structure rather than in terms of physiologic and clinical response. It

is quite possible that colloids having physiochemical properties at variance with the plasma proteins might prove to have advantages over plasma itself in special circumstances. A knowledge of the molecular structure, however, governing as it does the viscosity and osmotic pressure, is of great help in improving and perfecting a plasma substitute.

One of the most significant factors in peripheral vascular collapse, no matter what the cause, is the diminished circulating blood volume. Whole blood is usually the ideal replacement fluid, but there are some varieties of shock and shock-like states when some clinicians prefer a colloidal solution without erythrocytes and therefore use plasma. There are also times when blood is not obtainable, or not obtainable without some delay for blood grouping and cross-matching, or not in sufficient quantity to meet a specific need. In these instances plasma is better for injection than a non-colloidal solution such as isotonic sodium chloride which dilutes the serum proteins and diminishes the colloid osmotic pressure, resulting in a greater and more rapid escape of fluid from the vascular tree.

The proteins of plasma probably are utilized for several functions that one could not expect to find in a single substitute. The chief function, however, at which a substitute is directed is the oncotic one.

An acceptable plasma substitute should satisfy certain minimal physical, physiologic and immunologic criteria. The physical properties of such a substitute are: (1) stability, (2) ease of storage, (3) low viscosity, (4) high osmotic pressure, and (5) a colloidal particle size large enough to be retained in the circulation.

From a physiologic standpoint a plasma substitute must be safe for injection in large quantities, must be retained in the circulation long enough to be effective as an oncotic force, and should not interfere with the function of internal organs. Of these last functions attention should be turned especially toward blood

coagulation, the defense against infection, tissue repair, and the function of liver and kidneys.

Immunologically a plasma substitute should not be an antigen, or at most should be a poor one. If any antigenicity can be demonstrated, it should not be associated with any sensitivity to horse or rabbit serum. Any material intended for a plasma substitute should have a minimum of natural sensitivity and no associated food sensitivity.

Gum Acacia. Gum acacia is the one colloidal infusion material remembered from the first World War. This polysaccharide was used extensively until study of its toxicity, especially with reference to its antigenicity and its tendency to produce liver dysfunction and hypoproteinemia, placed it in disfavor.^{15,17,21,22,23}

In spite of its untoward side effects, solutions of gum acacia were good substitutes for the oncotic functions of plasma, and many investigations into its properties have provided the pattern for study of later substitutes.

Human Serum Albumin. One of the substitutes for plasma which was studied most extensively was human serum albumin. Being derived from plasma itself it is not a true plasma substitute in its sparing effect on blood donations. At the same time, since it is a fraction of plasma, it is subject to less criticism than artificial substitutes.

Safe and effective though human serum albumin may be, it was prepared originally for military use with mobile forces^{60,90,91} with relatively little regard to cost. Unless cheaper methods of fractionation can be achieved or the cost of human serum albumin subsidized, it seems improbable that it will enjoy wide clinical use in civilian medicine.

Serum albumin has a molecular weight of 69,000 (plasma protein average 90,000) and on a theoretical basis should hold 18 cc. of fluid in the blood stream per gram.⁷³ This theoretical measure of oncotic function has been confirmed by determinations of plasma volume increase

after infusion of the human serum albumin.^{9,45,87}

Albumin solutions have a high degree of thermal stability⁷⁴ and may be given intravenously with a very low reaction rate. Globulin deficiency after repeated infusions has been reported.³⁷ Following the injections of serum albumin there is a hemodilution which is well sustained in depleted subjects but which is transient in normal controls. Such hemodilution and plasma volume increase is most marked if additional fluids are given with the albumin. Fluids should be given with albumin infusion in dehydrated patients.³⁵

Scrum albumin is well retained if there is no hemorrhage or loss through burned surfaces.⁹ Infusions of albumin are effective in the treatment of shock and burns and are followed by an increase in right auricular pressure, arterial pressure and cardiac output.^{9,37,87}

Albumin is utilized like native serum protein, but only a small portion is retained in the circulation after injection, the remainder evidently being stored.³⁷ Hypoprotecinemia may be corrected if sufficiently large amounts are used.³⁵ Study of tissues following repeated infusion reveals no evidence of pathologic change.³⁷

Albumin has been used in the treatment of the nephrotic state; and while there is a definite increase in proteinuria following infusion, there is not always an accompanying diuresis.^{35,37} There is but temporary improvement in cirrhotics following infusion of human serum albumin.³⁷ A salt-free preparation has been made available which is a better agent, theoretically at least, for the mobilization of edema.⁷⁵

Gelatin. Gelatin solutions were used first as a plasma substitute by Hogan in 1915,²⁸ but were abandoned for several reasons. Bayliss,⁴ who had done much to establish gum acacia as an effective agent for the treatment of shock, objected to gelatin on the theoretical ground that all contaminating spores might not

be killed in its preparation. Other investigators used methods of preparation of solutions at variance with Hogan's and obtained different results which did much to discredit the earlier work.

Between the 2 wars gelatin was mentioned as a substitute for plasma only once. Wolfson and Teller,⁹² using the refractive index of serum, reported that infused gelatin was retained in the circulation long enough to be effective in post-hemorrhagic hypotension.

The more recent investigations into the suitability of gelatin as a plasma substitute indicated that it was both safe and effective as a substitute for the oncotic function of plasma in the treatment of shock and hemorrhage. Inasmuch as gelatin solutions are composed of molecular aggregates of varied size the question of optimum molecular structure became an important one. It was apparent that no gelatin would approximate closely the molecular configuration of the native plasma proteins so that the choice of a gelatin solution for use as a plasma substitute lay between a long and a short molecular chain structure.

The viscosity, gel strength, modulus of rigidity and temperature of solidification are directly proportional to the size of the molecular chain while the fluidity and melting point are inversely proportional to molecular chain size. The small molecules, while having a higher theoretical osmotic pressure than the large molecules, are lost rapidly through the kidneys so that the effective osmotic pressure is actually higher with the large molecular gelatin. The best preparations from the standpoint of physiologic response then have the practical disadvantage of high viscosity.

Gelatins of any molecular structure seem to be innocuous and safe for injection in large quantities.^{27,34,40,56} The absence of liver and kidney damage in both dogs and patients after infusion of gelatin has been demonstrated.^{40,47,56,63} More rigorous tests were used by Van Slyke³⁵ in which gelatin was given to animals

with renal ischemia. Recovery was as rapid and regular in the gelatin infused animals as in the controls. Morphologic changes found in animals after massive gelatin infusion and after repeated infusions in all instances were reversible.⁶⁸ Human autopsy material revealed no changes attributable to gelatin.⁴² Untoward reactions following gelatin infusion in human subjects are infrequent,⁴⁴ and the venous thrombosis found after some gelatin infusions was demonstrated to be due to a mercurial preservative.⁶⁵

Following the injection of gelatin intravenously there is an immediate rise in serum gelatin concentration and a concomitant fall in native serum proteins. The serum gelatin concentration diminishes gradually thereafter with a reciprocal rise in serum protein concentration. The speed of this reciprocal reaction is inversely proportional to the molecular size of the gelatin while the duration of detectable gelatin concentration in the blood is directly proportional to the molecular size.^{27,40,47,53,63}

Highly degraded (short molecule) gelatin may leave the circulation completely in less than 24 hours while minimally degraded varieties (long molecules) disappear completely only at the end of 5 days.^{27,40}

Blood coagulation is not effected following gelatin infusion,^{40,47} and although the hematocrit reading and the hemoglobin concentration are decreased, the total red cell volume is not diminished either in animals in shock or in normal unanesthetized controls.^{53,55} The sedimentation rate is increased markedly after gelatin infusion according to all observers.

The increased sedimentation rate seen with so many of the macromolecular colloidal substitutes for plasma is a measure of the degree of pseudo-agglutination of the erythrocytes. The phenomenon of pseudo-agglutination is apparently without deleterious effect insofar as gelatin is concerned, based on observations of oxygen transport^{62,63} and direct visualiza-

tion of capillaries after gelatin infusion through a rabbit's ear window.^{1,63}

The possibility of difficulty with the cross-matching of the blood of patients recently infused with gelatin (up to 4 days) was eliminated by the utilization of glycine to prevent the phenomenon of pseudo-agglutination in serum cell suspensions.⁴³

The use of various gelatin solutions in the treatment of experimental shock revealed differences resulting from the type of gelatin preparation used, but, in general, gelatin was found to be an effective agent for the restitution of colloidal osmotic pressure. Swingle and his associates^{39,80,81} found gelatin to be superior to saline and demonstrated pooled heparinized plasma to be no better than gelatin. Parkins⁶² work indicated that gelatin is among the best of the colloidal substitutes for plasma. Gordon, Hoge and Lawson²⁰ found gelatin to occupy an intermediate place between blood and crystalloids in its ability to maintain the circulation after blood loss. Winkler, Danowski and Elkington⁸⁹ found gelatin to be equal to serum in the treatment of salt depletion shock.

Attention has been called to the differences between gelatin types and molecular structure by several groups of investigators.^{27,38,40,41,56} Clinical superiority was claimed definitely for the long molecular structures by most observers,^{58,59} although it was recognized that the short molecular form was both effective and innocuous.

The excellent study from Whipple's⁷² laboratory revealed that gelatin caused no alarming disturbances; it produced both plasma protein and hemoglobin when given by mouth, produced blood protein equivocally when given by vein, and had no inhibitory action on the formation of plasma proteins from casein hydrolysates or amino acids when those materials were infused after gelatin. These studies were done with doubly depleted dogs (anemic and hypoproteinemic), and on the basis of the behavior

of these animals 2 questions were raised: the possibility of toxicity from gelatin when given over a period of 1 to 2 weeks and the possibility of gelatin infusion causing further damage in kidneys already diseased. The prolonged administration of gelatin is apparently without deleterious effect in patients,^{27,40,42,56} and it does not seem to alter kidney function adversely in the diseased or damaged kidney.^{27,40,42,44}

In normal individuals the administration of poorly degraded gelatin solutions is attended by an increase in cardiac output and by an increase in plasma volume, but not by a rise in arterial pressure.^{19,40} In the patient in peripheral collapse the same physiologic changes are seen, but the low blood pressure is rapidly returned to normal. In the shocked individual with depleted plasma volume 52 gm. of gelatin (P-20) in 1000 cc. of fluid increased the plasma volume for 4 to 6 hours to the same extent as did 50 gm. of human serum albumin.^{34,38,40,71} Plasma volume increases are greater but less sustained following gelatin infusion as compared with blood and plasma.^{42,71}

Poorly degraded gelatin solutions have been used as an agent for the mobilization of edema with variable results.^{6,44} The use of highly degraded (short molecule) gelatin in edematous states is not without danger because of the escape of small gelatin particles into the edema fluid.⁴² The larger gelatin molecules (P-20) pass through purposely injured capillaries only 35 to 60% as much as do the plasma proteins.⁵⁵

Of all the plasma substitutes, except those derived from plasma itself, gelatin is the only protein. Even though it is an incomplete protein, it is at least partially metabolized. Brunschwig⁷ demonstrated the metabolism of gelatin in animals and man,⁷ and Koop and his associates⁴⁶ found that when nitrogen is supplied as half gelatin and half casein or fibrin hydrolysate, the utilization of nitrogen was better than that achieved with the hydrolysate alone.⁴⁶

Two variations of gelatin solutions have been prepared as plasma substitutes: isinglass (iethyocolla) and oxypolygelatin.

Isinglass, a collagen prepared from the swim bladders of hake with 96.6% of its protein available as amino acids⁵ was studied by Taylor and his associates.⁸⁴ After animal experiments and clinical trial it was thought that a suitable animal gelatin rather than isinglass offered greater assurance of effective maintenance of blood pressure because of the much longer time it remained in the blood stream of the infused animal.⁸⁸

Oxypolygelatin, an oxidized, polymerized gelatin was introduced by Pauling⁶⁶ and developed to the point of reproducibility. Observations by Parkins⁶² indicate that the application of oxidation and polymerization procedures to ossein gelatin might increase its fluidity without serious change in its physiologic characteristics.

Bovine Albumin. Whole bovine plasma has been known to produce alarming reactions when given intravenously to other species.⁸⁶ Such reactions were associated with the globulin fraction of bovine plasma to a large degree.⁵⁰ Bovine albumin can be prepared in such fashion as to have a low reaction rate⁸³ and a non-bacterial chill-producing substance has been described in bovine albumin.⁴⁹ Reactions with the purified albumin when they do occur include urticaria, diarrhea, fever, nausea, vomiting and chill.⁸³

The bovine albumin is a potent antigen,^{24,32,52,52} and there is the possibility of cross-reaction with beef products taken by mouth.²⁵ In spite of this it has been administered to patients.^{10,16,36}

The infusion of a bovine albumin to animals in thermal shock is a therapeutic procedure not attended by toxic reactions but less effective than plasma when large and continuous protein and fluid losses are encountered.¹³ The plasma volume and circulatory tone are adequately maintained after infusion, and the ability of bovine albumin to hold

fluid is equal to that of human serum albumin.²⁶

Serum and urinary potassium are not significantly altered after infusion. The morphologic changes produced in rabbits following infusion of bovine albumin are all reversible, but this does not carry over to human subjects necessarily.³

Globin. A modified globin prepared from the erythrocytes of man has been used by Strumia and his co-workers⁷⁹ as a substitute for the colloidal osmotic functions of plasma. A preliminary report published by them in 1945 indicated that globin had these general attributes: (1) solubility in water at pH 7.4, (2) minimum solubility at pH 6.5, (3) a viscosity lower than that of citrated plasma, (4) a molecular weight of 85 % of the globin equal to 34,000, (5) a symmetrical molecule, (6) an approximate yield of 250 gm. per 1000 cc. of packed erythrocytes, (7) stability in solutions of 0.85 % saline (under ordinary conditions of preservation), (8) miscibility with citrated blood or plasma, (9) failure to increase erythrocyte sedimentation rate, and (10) production of hemodilution lasting 24 to 120 hours after intravenous infusion.

The authors found no evidence of antigenicity or toxic properties other than pyrogenic reactions and what they called a "pressor effect" and a "vasomotor effect." Globins exhibiting instability at pH 7.4 were not used in clinical investigations because of the embolic phenomena associated with death and organic damage encountered in animals when such globins were used.

The globin prepared by Strumia and his co-workers^{77,78,79} was reported by them to be satisfactory in the treatment of shock from trauma, hemorrhage and burns, in the correction of hypoproteinemia and in the treatment of edema in a patient with chronic glomerulonephritis.

Seegal⁷⁶ and his associates found human globin anaphylactogenic in the guinea pig. They found no reaction following human globin infusion in mice and rabbits, but dogs exhibited untoward reac-

tions characterized by erythema, urticaria, facial edema, dyspnea, hyperperistalsis, defecation and unsteady gait. Histologic section showed deposits of globin-like material in the proximal convoluted tubules of mice, rabbits and 1 dog within 2 days after injection which were not seen in animals sacrificed 8 days after injection.

Rhoads and Parkins⁶⁹ and their co-workers confirmed the results of Seegal and extended observations to include the tolerance of rats to rat globin and dogs to dog globin. They concluded that the efficacy of human and dog globin in treatment of hemorrhage in dogs, and rat globin in burn shock in rats showed globin to be less effective than saline. On the basis of these results observations were not extended to human subjects.⁷⁰

Hemoglobin. The early attempts at preparing a hemoglobin solution free from the stromata of erythrocytes resulted in an infusion material which elicited untoward reactions when given intravenously to animals.^{2,61} One of the most serious effects, the blockage of renal tubular lumina by hemoglobinous pigments, was eliminated by improved methods of preparation. Pure hemoglobin solutions when given intravenously are not attended by renal tubular changes^{11,12,61} if there is no preëxisting tubular damage.⁶⁴

Solutions of pure hemoglobin carry oxygen and maintain colloidal osmotic pressure for periods up to 36 hours after which they become ineffective because of transformation of hemoglobin to methemoglobin and the loss of injected hemoglobin through the kidneys.^{29,50} The erythrocyte sedimentation rate is increased after injection of hemoglobin. A hemoclastic crisis is seen soon after injection, and this is followed by a leukocytosis in 24 hours. No casts are found in the kidney, but deposits of hemoglobinous pigment can be seen in the liver and spleen.²⁹

Following the injection of pure hemoglobin solutions into the circulation of dogs there is a rise in blood pressure which cannot be accounted for on the basis of the

oncotic pressure of the hemoglobin solution alone. There is a 100% increase in oxygen consumption following hemoglobin infusion.⁵¹

Pectin. Solutions of pectin, a polysaccharide, were introduced as a substitute for plasma by Hartman and his associates in 1941.²³ Intravenous injection of pectin in animals and man was followed by no visible deleterious effects and it was non-antigenic.¹⁸ Bryant, Palmer and Joseph⁸ reported that intravenous infusions of pectin produced no changes in viscera of rabbits and that none was detectable in the blood 7 days after injection. Hueper,³⁰ on the other hand, refuted these findings by demonstrating in both animals and man that even partially degraded pectin is retained in liver, kidney, bone marrow, spleen and arteries. Histologic changes included foam cellular formations, hyaline necrosis, foreign body giant cells and calcium incrustations.

Following the intravenous administration of pectin in normal human subjects, the sedimentation rate is increased; the hematocrit falls more than the hemoglobin concentrations; the albumin-globulin ratio is unaffected and the arterial and venous pressure is slightly increased.⁴⁸ Plasma volume increases persist 4 hours after infusion.³³

On the basis of animal experiments, Middleton and Wiggers believed that the

usefulness of pectin was limited to the early period of posthemorrhagic hypotension. They found no correlation between hemodilution and favorable response which suggested a possible deleterious influence when used after severe hemorrhage.⁵⁷

As a substitute for plasma, pectin was found to be inferior to serum,¹⁸ less safe than gelatin,⁶⁶ and no better than saline in posthemorrhagic prolonged hypotension.¹⁴

Methyl Cellulose. Like polyvinyl alcohol, methyl cellulose has not enjoyed wide use as a plasma substitute. The material that has been given trial is a methyl ether of cellulose and consists of long chains of dextrose molecules with a characteristic high viscosity and a molecular weight of about 50,000. It is effective in shock in animals and is non-antigenic but exhibits the phenomenon of excessive storage in the viscera.^{3,31}

Summary. Of the plasma substitutes studied extensively during the recent war years only human serum albumin and gelatin solutions seem to be both safe and effective on the basis of reports available at this time. Human serum albumin derived from plasma itself, is not, strictly speaking, a substitute. Gelatin, in addition to being safe and effective, is also cheap, and when fortified with amino acids or protein hydrolysates is a readily available source of parenteral protein.

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OPHTHALMOLOGY

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EXOPHTHALMOS OF ENDOCRINE ORIGIN

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THE concept of the mechanism of production of exophthalmos, with particular reference to thyroid disorders, has not yet reached the stage of universal agreement. There have, however, been significant changes and developments in the past few years and this seems an opportune time to review these changes. Three important articles have been published in the past 2 years which endeavor to correlate our present knowledge, both clinical and experimental, of the production of exophthalmos. There are 2 groups of cases which present different clinical features but which, with advancement of our knowledge, seem to have a single etiologic basis. In the average case of so-called exophthalmic goiter the eye changes are not of particular moment or concern. Much of the change in appearance and of the subjective ocular symptoms is the result of retraction of the lids rather than actual protrusion of the globe. This is true particularly in individuals with other manifestations of definite hyperthyroidism. However, in certain other individuals with thyroid disease, exophthalmos develops progressively which may lead to extreme protrusion of the globe, chemosis of the conjunctiva, inability to close the lids, resultant exposure-ulceration of the cornea, and at times loss of the eye. These cases occur in individuals with both hyper- and hypothyroidism, the extremes ranging from severe thyrotoxicosis to frank myxedema. This latter group of cases

with exophthalmos has had a variety of terms applied to it: among the most commonly used are malignant exophthalmos, progressive exophthalmos, exophthalmic ophthalmoplegia, postoperative progressive exophthalmos, special ophthalmopathic type of Graves' disease, and thyrotropic exophthalmos. The reasons for placing this group apart from simple exophthalmic goiter are many. There is a different age and sex relationship, a difference in response to treatment and different findings in the orbit. Exophthalmic goiter affects young adults chiefly and is more common in women than in men. Progressive exophthalmos affects middle aged adults and men are more common in this group than women according to reports by Mulvany.⁹ The urine of patients with ordinary exophthalmic goiter shows little or no thyrotropic activity while that of patients with progressive exophthalmos contains an excessive amount of thyrotropic substance. In general, the proptosis and lid retraction of exophthalmic goiter recedes following thyroidectomy, although an immediate postoperative increase has been noted by Dobyns³ and others. Thyroidectomy usually has the opposite effect on progressive exophthalmos, increasing the proptosis and often leading to acute embarrassment of orbital circulation, ocular motility, and even of vision itself.

There has been a tendency in the past to consider that 2 different mechanisms

are involved in the production of these 2 apparently different types of exophthalmos. From recent clinical and experimental investigations, however, it would appear more logical to assume that the exophthalmos does not differ fundamentally in type but only in course and degree, and that this difference in course and degree depends upon the presence or absence of a compensatory mechanism for the control of the production of an exophthalmos stimulating substance. It seems likely that the pituitary produces the substance that is responsible for exophthalmos and that the substance for its control is elaborated in the thyroid. Originally it was thought that both the retraction of the lids and the proptosis might be explained on the basis of sympathetic stimulation brought about by excess secretion of thyroxin. Sympathetic stimulation causes exophthalmos in certain animals, but this mechanism is undoubtedly not active in man. Increased sympathetic tone may well account for lid retraction alone; but, as shown by Pochin,¹⁰ exophthalmos cannot be produced in man by sympathetic stimulation. It has been known for many years that extracts of the anterior pituitary, containing thyroid stimulating hormone, cause exophthalmos. According to Means,⁷ this was first demonstrated by Schockaert in 1931 and has been amply confirmed and elaborated upon. Pituitary extracts generally produce an initial rise in metabolism accompanied by exophthalmos. This exophthalmos is enhanced by thyroidectomy, but animal experimenters have never produced exophthalmos which is exactly comparable to the severe progressive type seen in man.

Long continued exophthalmos produced in animals by pituitary extracts is reported to lead to permanent changes in the extra-ocular muscles according to Aird.¹ Other factors are also of importance in experimental exophthalmos. Marine believes that the gonads seem to play a rôle, for castration lessens the exophthalmos produced by thyrotropic hormone in certain animals and testosterone brings it back.

Recent work by Dobyns³ has shown that thyroidectomy alone causes an increased prominence of the eyes of guinea pigs. Smelser¹⁴ demonstrated that the exophthalmos produced by thyrotropic hormone in thyroidectomized guinea pigs seems to be due chiefly to an increased water content of orbital fat and extra-ocular muscles and that this same change is not noted in muscle or fat of other parts of the body. Neither thyroidectomy alone nor thyrotropic hormone produced this result. Rundle and Pochin¹¹ found marked increase of the fat content of the extra-ocular muscles in human exophthalmos-associated with Graves' disease. These experimental studies would seem to indicate that the pituitary thyrotropic hormone is the agent responsible for the production of exophthalmos. The rôle that the thyroid plays as a controlling factor in the production of this hormone seems also to have been shown. From the clinical standpoint the recent works of Means⁷ and Mann⁵ would seem to substantiate these conclusions while the work of Mulvany⁸ seems opposed at least in part.

Mulvany, along with others, believes that the exophthalmos in exophthalmic goiter is due to an overactive sympathetic nervous system. He explains retraction of the lids as due to stimulation of Müller's tarsal muscle and exophthalmos as due to the combined pull of Müller's and Landström's muscles opposed by weakened extra-ocular muscles. Mulvany states that these 2 sets of unstriated muscles exert a direct and an indirect pull on the globe, and that the weakness of the voluntary extra-ocular muscles is due partly to thyrotoxic myasthenia and partly to atonia caused by local neuromuscular degeneration. That sympathetic overactivity is the rule in hyperthyroidism cannot be doubted, but it seems that undue emphasis is placed upon the very small essentially vestigial unstriated muscles in the orbit as they exist in man. In progressive exophthalmos, Mulvany⁸ states that retraction of the lids is due to enlargement of the levator muscle and that

exophthalmos is the result of an increase of the orbital contents. This author describes different microscopic findings in the 2 varieties of exophthalmos. In cases of exophthalmic goiter of the usual type he finds widespread neuromuscular degeneration, occasional infiltration of round cells, fat infiltration, and some fibrous replacement in the disintegrating muscle and nerve cells. In malignant exophthalmos he finds enlargement of the muscles, fibrosis which is often widespread through the muscles, edema, degeneration, and round cell infiltration. This author emphasizes the contrast between the 2 processes but, as Mann states, it seems possible that one could be an early and the other a late and more extensive phase of the same pathologic process.

In contrast to the hypothesis advanced by Mulvany, Means,⁷ and Mann⁵ believe that probably these 2 types of exophthalmos have a single basis. This basis is the production of excessive amounts of thyroid stimulating hormone by the pituitary perhaps initiated, as Means states, by nervous stimulation through the hypothalamus. On this basis, this excessive secretion of thyrotropic hormone by the pituitary causes the normal thyroid to respond with hypertrophy and excessive secretion of thyroid hormone and initiates the production of exophthalmos. Along with these changes there is present a certain degree of sympathetic hypertonia and of myasthenia, perhaps on the basis of concomitant alterations in the adrenal and thymus or perhaps due to the excessive thyroxine alone. The excessive thyroid hormone, besides stimulating metabolism, acts as an inhibiting mechanism on the pituitary causing lessened production of thyrotropic hormone. Thus the exophthalmos does not become excessive because the thyrotropic hormone, although produced in a supernormal amount, is controlled by a regulatory mechanism. The degree of exophthalmos present may vary from moderately severe in some cases to none in others; the latter cases exhibiting only lid retraction and perhaps some weak-

ness of the ocular muscles. An intractable progressive type never results. In the case of progressive exophthalmos the excessive amount of thyrotropic hormone is produced as before; but, instead of stimulating normal thyroid tissue, for some unknown reason the thyroid in these cases seems unable to respond normally with the production of large amounts of thyroid hormone. Uninhibited by excessive hormone from the thyroid the pituitary goes on to secrete still more thyrotropic hormone. The exophthalmos continues to increase and when the process is of long enough duration and sufficiently severe, the pathologic changes present in the ocular muscles become irreversible. There are obviously a number of suppositions in this hypothesis. Just where the abnormality is present in the usually self-regulatory mechanism is open to question, but some recent works with thiourea derivatives may give a clue. Thiouracil apparently exerts its action by interfering with the production of thyroid hormone by the thyroid gland, and the resulting deficiency of thyroid hormone directly or indirectly stimulates the anterior lobe of the pituitary. The increased secretion of thyroid stimulating hormone by the anterior lobe induces thyroid hyperplasia.⁴

Means states that hyperplasia of the thyroid may be obtained in rats by treatment with sulfathiazole and exophthalmos results which persist after death. In man, sulfoeyanate therapy may cause hyperplasia of the thyroid with hypofunction and the same author states that exophthalmos may occur. The following is a quotation from Means relative to the production of exophthalmos in these cases: "It is not clear precisely where such agents impinge upon the pituitary-thyroid axis, but the weight of evidence is that it is on the thyroid directly, imposing some obstruction to the completion of the elaboration of thyroid hormone. The organism thus becomes hypothyroid, which serves as a stimulus to the pituitary to increase its output of thyrotropic hormone, which, in turn, causes the thyroid to become hyper-

plastic and the eyes to become protruded. The hyperplasia of the thyroid, however, is ineffective because the obstruction to completion of thyroid hormone persists." It may be that such an obstruction to thyroid hormone production exists in all cases of progressive exophthalmos, the degree of obstruction determining the degree of hypo- or hyperthyroidism present.

In Mann's recent work she has presented a series of case reports in an attempt to disentangle the parts played by the thyroid and pituitary, respectively, in individual patients. The cases are divided into 3 groups on the basis of their most prominent symptoms. The first group contains patients who show primarily a deficiency of thyroid hormone with a compensatory excess of thyrotropic hormone. In the second group the cases show a primary excess of thyroid hormone, which, later, as the result of thyroid atrophy or removal is replaced by excess thyrotropic hormone. The third group shows symptoms of excess thyroid hormone and excess thyrotropic hormone arising simultaneously. On the basis of this study Mann concludes that the signs of excess thyroid secretion include loss of weight, rapid pulse, raised B.M.R., moist skin, lid retraction, and lid lag. Excess thyrotropic hormone leads to symptoms consisting of orbital muscle, lid, and conjunctival edema and infiltration which results in proptosis, ophthalmoplegia and fundus changes. Lid edema, chemosis and eversion of the conjunctiva are also the result of the orbital edema. All of these latter changes may or may not be associated with a deficiency of thyroid hormone. If this is present, it will show itself as low B.M.R., a gain in weight, thick coarse skin and slow pulse.

Agreement is by no means reached as to treatment of these obstinate cases of exophthalmos. The management of these cases of progressive exophthalmos taxes the ophthalmologists resources to the utmost and any advance in therapy is eagerly sought after. Attempts to treat the condition from an etiologic standpoint are still in their infancy and reports are insuffi-

cient to evaluate their true position at the present time. Thyroid hormones in large doses has been used with fair success, the beneficial results supposedly coming from inhibition of pituitary secretion. In the article by Mann thyroid therapy and surgical procedures designed to close the lids were used in these cases which did not exhibit marked hyperthyroidism. The end-result in these cases was exceptionally gratifying. Attacking the problem of reducing the pituitary secretion, Brain² has used ovarian follicular hormone in large doses with good success. He gives 50,000 units of progynon B every 5th day to both sexes and states that "exophthalmos usually diminishes." He reports that 1 early case of exophthalmic ophthalmoplegia made a complete recovery under this treatment. Direct irradiation to the pituitary in order to reduce its secretion has been tried by several investigators, including those at the Mayo Clinic, with rather disappointing results. We have attempted treatment with thyroid hormone and iodine combined in an effort to maintain the basal metabolism at a normal level. Results somewhat less striking than those shown by Mann have been obtained. Agreement, however, is almost universal concerning one point in the treatment of these cases and this point is the inadvisability of performing thyroidectomy. The group of cases presenting early symptoms of progressive exophthalmos must be weeded out of routine hyperthyroid patients if disastrous results are to be avoided. This point is especially stressed by Salter and Soley,¹² and by Means. The former authors recommend Roentgen ray therapy to the thyroid if symptoms of hyperthyroidism are prominent and if the condition of the patient demands treatment along this line. Thiouracil and radioactive iodine have also been advocated in treating this group of patients. Many authors advise decompression operations on the orbit in the severe cases of exophthalmos especially when the vision is at stake. The Naffziger operation is

the one most frequently employed but it cannot be undertaken lightly for the operation still remains a somewhat formidable procedure. Recently an alternative operation has been advocated by Schall and Reagan¹³ who perform a radical external ethmoidectomy. They believe that this operation should be carried out more frequently and observed, in their cases, a reduction of exophthalmos of 3 mm. They

state that, opposed to the Naffziger procedure, their operation is less formidable, produces a less disfiguring scar, creates an actual rather than a potential space, and does not result in a pulsating globe. Decompression operations of these types usually are not advocated until it has become obvious that the exophthalmos is progressing to a dangerous point in spite of adequate medical management.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF DECEMBER 15, 1946

A New Concept of Competitive Inhibition of the Renal Tubular Excretion of Penicillin. KARL H. BEYER, PH.D., M.D., HORACE F. RUSSO, B.S., ELIZABETH A. PATCH, B.S., and A. KATHRINE MILLER, PH.D. (Depts. of Pharmacol. and Bact., Med. Res. Div., Sharp & Dohme, Glenolden, Pa.). It has been established that penicillin is excreted both by the renal tubules and by glomerular filtration. The renal clearance of penicillin is normally about 5 times glomerular filtration rate.

The tubular transport mechanism for penicillin, p-aminohippurate (PAH) and Diodrast excretion is functionally the same. It has been reported that on a mass action basis one could competitively inhibit the tubular excretion of penicillin by saturating with PAH at high blood levels the functional capacity of the mechanism.

Caronamide, 4' - carboxy - phenylmethanesulfonamide,* effects a substantial physiologic economy of penicillin on an essentially different basis. It appears that the mode of action of this agent is to halt the transport mechanism responsible for the tubular excretion of penicillin and PAH.

Certain of the pharmacologic characteristics of caronamide are: (1) It is rapidly absorbed when administered orally, and may be given by this route to inhibit the tubular excretion of penicillin administered orally or parenterally. (2) Its renal elimination is limited essentially to glomerular filtration. (3) Its action is to inhibit the excretory transport mechanism *per se* for the tubular excretion of penicillins F, G, K and X, and PAH. (4) The effect of the agent

appears to be limited to a functionally single transport mechanism, for caronamide does not influence the Tm of glucose or arginine, the clearance of creatinine, urea, sulfadiazine, sulfathiazole, or the kidney volume of dogs at blood levels sufficient to suppress completely the tubular excretion of penicillin. (5) The compound has a low order of acute and chronic toxicity.

The efficacy and safety of caronamide have been substantiated clinically.

The Hyperpnea Produced in Normal Man by Maximal Voluntary Hyperventilation, by Inhalation of CO₂ and by Severe Muscular Exercise. J. H. COMROE, JR., M.D., and ROBERT D. DRIPPS, M.D. (Depts. of Pharmacol., Surg. Res., Anesthesiol., Med. Sch.; Physiol. and Pharmacol., Grad. Sch. Med., Univ. of Penna.). These experiments were designed to measure and compare (a) the maximal minute volume of respiration of which man is capable by voluntary effort (the maximal breathing capacity), (b) the maximal minute volume produced by CO₂ inhalation, and (c) that produced by severe muscular exercise in normal physically fit young men. The results of these experiments are shown in Table 1.

So far as the CO₂ inhalations are concerned the data show marked individual variations from subject to subject which is presumably due to differences in sensitivity of the medullary respiratory centers. Inhalation of 10.4% CO₂ produced maximal ventilation which was only 46% of the subjects' total breathing capacity. It is probable that CO₂ inhalation might have led to greater

* Sharp & Dohme has applied its trademark "Retentin" to this compound.

hyperpneas if certain inhibitory factors were not acting. These factors include inhibition of respiration (a) arising from the pressure receptors of the carotid sinus and aortic arch in response to the hypertension produced concomitantly and (b) due to narcosis of the centers by a direct depressant effect of high concentrations of CO₂ (of the 31 subjects breathing 10.4% CO₂, the following symptoms suggestive of central nervous system depression occurred: dizziness in 13, faintness in 7, unconsciousness in 3, symptoms resembling induction of anesthesia with nitrous oxide in 2, and analgesia in 1).

Sarcoidosis, and Carcinoma. FLORENCE B. SEIBERT, PH.D., MABEL V. SEIBERT, A. JANE ATNO, A.B., and HAROLD W. CAMPBELL, M.D. (Henry Phipps Inst., Univ. of Penna.). Electrophoretic analyses of sera, combined with chemical analyses for polysaccharide, can be helpful in the differential diagnosis of tuberculosis, sarcoidosis and carcinoma. Cases of tuberculosis were carefully selected in the clinic according to their stage of the disease. The carcinoma cases included lesions of many different organs, and 4 of the sarcoidosis series were verified by study of biopsy material. At least 20

TABLE 1

<i>Procedure</i>	<i>Subjects</i>	<i>Maximum average</i>	<i>Maximum range</i>	<i>Std. dev.</i>	<i>%</i>
Maximal breathing capacity .	19	166	132-198	20.3	100
CO ₂ 7.6% .	42	52	24-102	18.4	31
CO ₂ 10.4% .	31	76	40-130	24.8	46
Muscular exercise .	19	110	80-140	18.3	66

Muscular exercise produced more hyperpnea in 18 of 19 subjects than did inhalation of CO₂. The small changes in arterial CO₂ tension occurring in muscular exercise cannot account for the marked hyperpnea of muscular exercise.

The minute volumes at which dyspnea occurred in subjects breathing CO₂ were noted. In the group that experienced no dyspnea, maximal minute volumes ranged from 24 to 114 liters per minute (average 60); in those who experienced mild to moderate dyspnea, the minute volumes were 29 to 110 (63) and in those who noted marked dyspnea, the minute volumes were 50 to 130 (87). This emphasizes the fact that dyspnea is a subjective phenomenon not necessarily related to the volume of respiration. Some subjects did not notice hyperpnea in themselves until ventilation reached 30 to 40 liters per minute. It is therefore often desirable to measure both rate and minute volume of respiration in certain clinical cases.

cases of each type of disease were studied and the following conclusions were based upon the statistical analysis of the results.

Significant changes occurred in certain of the constituents of the blood, which appeared characteristic for the different diseases or different stages of disease. Some of the most conspicuous of these changes were the following: A rise in the gamma globulin occurred in the serum in minimal active tuberculosis, with a corresponding decrease in albumin. In moderately advanced disease the α_2 globulin and polysaccharide content also increased. These changes were still further emphasized in far-advanced tuberculosis and the other globulins were also increased. No deviation from the normal occurred in minimal tuberculosis of questionable clinical significance. Moderately advanced tuberculosis of questionable clinical significance showed only a decrease in albumin, indicating that it was the last component to return to normal. Sera from cases of sarcoidosis showed an increase in total protein, a proportionate large increase in gamma globulin and only a moderate increase in polysaccha-

Variation in Protein and Polysaccharide Content of Sera in Tuberculosis,

ride content. In carcinoma there was a decrease in total protein, a large increase in α_2 globulin and beta globulin and polysaccharide content.

It is suggested that the increase in gamma globulin in minimal tuberculosis may indicate antibody formation, whereas the rise in α_2 globulin and simultaneous rise in polysaccharide in advanced tuberculosis and carcinoma may represent tissue destruction.

The Non-participation of 1(+) Citrulline as an Intermediate in the Synthesis of Urea by Rat Liver Slices. JOHN H. NODINE and JOHN M. BUCHANAN, PH.D. (Dept. of Physiol. Chemistry, Univ. of Penna.). Since Krebs and Henseleit (*Ztschr. f. physiol. Chem.*, 210, 33, 1932) postulated the "ornithine cycle" as the main metabolic pathway of urea formation, numerous investigations have been undertaken to substantiate or disprove this hypothesis. The purpose of this present study is to test the hypothesis directly using isotopes. Rat liver slices were incubated in a medium containing isotopic bicarbonate (C^{13}) buffer, NH_4Cl , dl-ornithine and other ionic constituents as described by Krebs, both in the presence and absence of large amounts of 1(+) citrulline. The urea synthesized contained 2.08 and 2.19 atoms % excess C^{13} with and without citrulline respectively. The citrulline isolated at the end of the reaction showed no excess C^{13} . Evidence for adequate mixing of intra- and extracellular citrulline was presented by Krebs and others who showed an acceleration of urea formation (an intracellular process) upon the addition of citrulline to a medium similar to ours, and Gornall and Hunter (*J. Biol. Chem.*, 147, 593, 1943), who showed that citrulline accumulates in a medium containing liver slices and ornithine, the former showing diffusion into the cell, the latter showing diffusion out of the cell. It was thus concluded that 1(+) citrulline is not a major intermediate in the synthesis

of urea from CO_2 and NH_3 in rat liver slices under the conditions of our experiments. Calculations from the C^{13} concentration of the medium showed that 90 to 100% of the carbon of the urea formed was derived from the CO_2 of the medium. Thus the added citrulline was not converted to urea to any significant extent under the conditions of our experiments. A 3-fold acceleration of urea formation was noted upon addition of the citrulline to the reaction mixture. It was concluded that under the conditions of our experiments urea was not synthesized by the "ornithine cycle" as presently postulated.

The Effect of Inhalation of High and of Low Oxygen Concentration Upon Human Respiration and Circulation. ROBERT D. DRIPPS, M.D., and JULIUS H. COMROE, JR., M.D. (Depts. of Pharmacol., Surg. Res., Anesthesiol., Med. Sch.; Physiol. and Pharmacol., Grad. Sch. Med., Univ. of Penna.). Sixty-eight normal human subjects were permitted to breathe some of the following: 100% oxygen, 20.9, 18, 16 or 14.5% oxygen in nitrogen. Pulse rate and respiratory minute volume were recorded. In 28 of 33 subjects studied during the change from room air to 100% oxygen, a small immediate decrease in respiratory minute volume or pulse rate was observed. Average respiratory minute volume was depressed 3.2% and pulse rate 3.7% during the first 2 minutes of 100% oxygen inhalation. Statistical analyses of these data revealed a likelihood that the respiratory changes might have occurred by chance in 1 of 15 instances, a figure below the 1 in 20 normally regarded as significant in medical statistics. The possibility of the pulse rate changes occurring by chance was less than 1 in 1000, a highly significant observation.

If this change can be attributed wholly to a functional denervation of oxygen-sensitive receptors in the carotid and aortic bodies, these data suggest that

some chemoreceptors are tonically active at the oxygen tension present in the arterial blood of many normal men breathing room air at sea level. The small degree of the changes indicated that they are only minimally active.

Fourteen subjects breathed 18% oxygen and 21 breathed 16% oxygen after control data on expiratory minute volume and pulse rate had been obtained with room air. An increase in pulse rate was a more sensitive index of anoxemia than was an increase in respiratory minute

volume. Of the subjects, 79% showed an increase in pulse rate with 18% oxygen, and only 36% showed increased ventilation (5% increases above control values).

Our data indicate that the human circulatory system is usually stimulated by reducing the inspired oxygen percentage from 20.9 to 18, but respiration is stimulated in only a few individuals breathing 18 or 17% oxygen and is not increased in the majority until 16% oxygen is inhaled.

BOOK REVIEWS AND NOTICES

NUTRITION AND CHEMICAL GROWTH IN CHILDHOOD. Vol. II. Original Data. By ICIE G. MACY, PH.D., Sc.D., Director of the Research Laboratory, Children's Fund of Michigan. With a Supplement by JULIA O. HOLMES, PH.D. Index to Vols. I and II. Pp. 1044; 1081 ills. and figs. Springfield, Ill.: Thomas, 1945. Price, \$10.00.

Four years ago Dr. Macy and his associates presented Vol. I of *Nutrition and Chemical Growth in Childhood*, in which were stated the conditions under which the 10 year study was conducted, the methods employed to secure the samples and data and their statistical treatment.

Vol. II, titled "Original Data," may be divided into 3 parts: the data obtained by the Research Laboratory of the Children's Fund of Michigan, similar data obtained by Dr. Julia Holmes (formerly associated with Dr. Macy) at The Department of Home Economics of the University of Illinois on pre-school children, and comparative data on certain abnormal cases studied by the Michigan group by their research methods which were referred by the Children's Hospital.

Within the confines of a necessarily brief review it is impossible to analyze and evaluate the mass of data here presented. Inaccuracies and incongruities will be pointed out by future workers in these fields. Certainly very few typographic or gross errors are apparent.

The original material consists of thousands of data obtained in the course of studying serially a number of normal children living at the Methodist Village. These data are concerned with the foods ingested, and analyses of urine and feces. For each child at each period of observation there are also records of physical examination, psychological and endocrine estimations, anthropometric measurements, basal metabolism, activity, laxation rates, emotional reactions, blood studies and dental conditions, etc., which are correlated with the balance studies. Even the climatologic conditions have been recorded.

One feature of these observations which when assembled would comprise a valuable

monograph is the presentation of serial growth roentgenograms of the bones, the teeth and the gastro-intestinal tract following the use of various test meals. The reproductions of these films are amazingly clear.

If one could point to any aspect which is below the average in value and excellence, this Reviewer would suggest that the psychological and so-called endocrine studies add little to the mosaic and are not of equal value.

About 60 pages are devoted to the studies of Dr. Holmes and the Illinois group on 5 girls who were studied for 32 consecutive weeks, and on 7 boys studied for 72 weeks. Nitrogen, phosphorus and calcium balances related to growth and skeletal structure were the special objects of these studies.

A prominent feature of the "Original Studies," expanded in the Addenda is the assemblage of data on the blood in health and disease.

In the course of Dr. Macy's work, certain disease conditions well suited for study by the methods used were admitted to the Children's Hospital. These cases are also presented in the Addenda and include Osteoparathyrosis, ununited fracture, lipemia and epilepsy.

The material in this volume should prove authoritative and valuable for workers in growth or nutrition as well as chemistry. They should supplant data which have been obtained from animals. The data would seem to be especially timely in view of the nutritional conditions which exist and must be corrected in a scientific way in the war-torn countries of Europe and Asia. Expected results of food relief can be based on and compared with the work of Dr. Macy.

E. T.

PREVENTIVE MEDICINE AND PUBLIC HEALTH. By WILSON G. SMILLIE, M.D., Professor of Public Health and Preventive Medicine, Cornell University Medical College. Pp. 607; 41 ills. New York: Macmillan, 1946. Price, \$6.00.

This volume is written from the point of view that preventive medicine is an essential part of the practice of medicine. Care-

ful examination of the text reveals the clear, concise and comprehensive manner in which the author has fulfilled this aim.

Teachers, students and physicians who have been in the habit of going to this author's volume "Public Health Administration in the United States" for general information in the field, and especially to find a terse, satisfying, opinion upon controversial matters, will find the same dependable quality here.

In his Preface the author admits that "the whole broad field of the social aspects of medical care has been presented most inadequately." This apparent modesty must not be misunderstood; it is actually a result of his exhaustive and persistent literary and personal research undertaken to find practical and intelligent solutions for matters which "are still a fluid concept that is not ready for presentation in textual form." Nevertheless, the chapter on "Adequacy of Medical Care" is a superior production.

The text is dedicated to Lemuel Shattuck, a Boston bookseller whose studies in vital statistics of New England aroused his concern for public health and preventive medicine. His report, published in 1850, became a foundation stone upon which even our current programs might well be built. Each section of this volume is introduced by a remarkably modern quotation from Shattuck's report.

The book is an attractive one both in appearance and in diction. It can be recommended as a dependable guide for the physician, the student and the public health official.

A. H.

SYNOPSIS OF NEUROPSYCHIATRY. BY LOWELL S. SELLING, Sc.M., M.D., Ph.D., Dr.P.H., Director, Psychopathic Clinic, Recorder's Court, Detroit, Mich.; Associate Attending Neuropsychiatrist, Eloise Hospital; Adjunct Attending Neuropsychiatrist, Harper Hospital. Pp. 500. St. Louis: Mosby, 1944. Price, \$5.00.

THE new book shelves of our medical libraries have been carrying an ever increasing number of volumes with such titles as psychiatry, neuropsychiatry, physiologic psychology, medical psychiatry, mental disorders, mental hygiene, psychopathic personality, psychosomatic medicine, etc.

While one would hardly question an author's rationale in limiting the field of

discussion under his particular title, there is little doubt that each author does differ in his own conception to a degree that gives rise to a great variety of meanings and interpretations based on his own training and experience. This trend has led to enough confusion in this field to excite comment at the Centennial Meeting of American Psychiatric Association in Philadelphia. A member arose and asked for the formation of a committee to establish definition of terms that would find greater agreement amongst a wider variety of workers in the field. While small active groups in confined areas may understand each other, the less active (in research) and more remote by location have found great difficulty in understanding the newer connotations of the language. Nothing apparently came of the proposal.

While reviewing the "Synopsis" it occurred to the Reviewer that here was a book that can, more or less, do what the "Unformed Committee" may have accomplished.

The "Synopsis" provides a means of attaching oneself to the basic concepts with which newer ones can be compared or associated. The elements of neuroanatomy and neuropathology described serve as a basis of understanding the organic neurologic syndrome discussed. An extensive review of psychopathology, abnormal psychology and psychoanalysis presents a fine background for functional disorders.

The book is divided into 2 parts: Neurology, 10 chapters, with a total of 296 pages, and Mental Disorders, 15 chapters, totaling 177 pages. The classification of personalities is given a modern touch in describing such personalities as "Caspar Milquetoast," "wolves," "fairies" and "screwballs."

J. S.

SYNOPSIS OF PHYSIOLOGY. By ROLLAND J. MAIN, Ph.D., Professor of Physiology, Medical College of Virginia. Pp. 341; 21 ills. St. Louis: Mosby, 1946. Price, \$3.50.

THIS small book aims to be a text for review purposes for students with some knowledge of physiology and of medicine. The book covers a wide field in an extremely brief form and is clearly expressed. There are relatively few figures but these are very clear diagrammatic presentations of material. The book is likely to have a considerable use by students who want to revise for

examinations. In this respect it will be very useful.

Apparently clinicians also request "a little book which hits the high spots." The Reviewer believes that such use would be a retrograde step in education. Knowledge should be used and be integrated into ever more comprehensive patterns. It is the thinking about interrelated facts that is important rather than the memorizing of such facts. The author has unquestionably thought considerably, but the brief statement does not encourage the reader to go beyond the author and to utilize his own imagination. Consequently the Reviewer finds himself diametrically opposed to the principle of such a book for use of medical graduates.

H. B.

DIAGNOSIS AND TREATMENT OF PULMONARY TUBERCULOSIS. By MOSES J. STONE, M.D., Assistant Professor in Medicine, Boston University School of Medicine; Instructor in Medicine, Tufts Medical School; Physician-in-Chief, Chest Clinics, Beth Israel and Massachusetts Memorial Hospitals; and PAUL DUFAULT, M.D., F.A.C.P., Superintendent of the Rutland State Sanatorium, Rutland, Mass. First 2 editions by Hawes and Stone. Pp. 325; 93 engravings. Philadelphia: Lea & Febiger, 1946. Price, \$3.50.

BECAUSE of the decreasing number of physicians and students interested in prolonged training in tuberculosis, there is need for a concise, comprehensive text on basic concepts and treatment of pulmonary tuberculosis. The authors of this book have produced an easily read and lucid guide in diagnosis and treatment. It is to be recommended to medical students and general practitioners as an elementary treatise in phthysiology. For those interested in broader training in this field a supplemental list of suggested reading is appended at the conclusion of each chapter.

Certain improvements could be made in the section on specific therapy. A treatise on this subject in 1946 might well include at least brief mention of streptomycin. In discussing the treatment of laryngeal tuberculosis, where so little can be offered the patient, the promising results of sulfa drug and penicillin insufflation should be noted. The sections on collapse therapy should

have discussed pneumoperitoneum as an adjunct in therapy and not merely as a possible complication of artificial pneumothorax.

The arrangement of the chapters is good, and the authors have accomplished their object in commendably short space.

S. S.

THE BIOLOGY OF SCHIZOPHRENIA. By R. G. HOSKINS, Ph.D., M.D., Director of Research, Memorial Foundation for Neuro-Endocrine Research, Harvard Medical School and Worcester State Hospital. Pp. 191. New York: Norton, 1946. Price, \$2.75.

In reference to the vast amount of human distress and of the unproductive expense resulting from schizophrenia, it is said one-fifth of all hospitalized patients in the country and almost 10% of state tax (Massachusetts) is required to care for the victims of this disease. Continuing the study of the condition as one of disordered biology, the writer discusses his thesis in the following sections: The Biology of Man in Relation to Schizophrenia; The Pattern of Schizophrenia; Psychosomatic Aspects of Schizophrenia; A Biological Appraisal of Schizophrenia.

These distorted personalities are most apt to develop in inadequate and frustrated people. As to cause—there is the possibility "that adequate studies of the enzymes might disclose a genuine pathology for the psychosis." After studying the nature of man, the pattern of the disorder is compared with that of other biologic patterns; and finally there are considered the chief functional deviations frequently observed in the endocrines, oxygen and carbohydrate metabolisms, and the circulatory system.

The writer's approach to the subject is unusual and stimulating.

N. Y.

DIGITALIS AND OTHER CARDIOTONIC DRUGS. By ELI RODIN MOVITT, M.D., CAPT., M.C., A.U.S.; Internist, Veterans Administration Facility, San Francisco. Pp. 204; 24 ills. New York, Oxford Univ. Press, 1946. Price, not given.

THE subject matter of this book includes digitalis leaf (purgarea) and various glycosides, digitalis lanata and lanatoside C,

strophanthus and its derivatives, squill and various other so-called cardiotonic agents of plant and animal origin. Historical data, source and chemical structure, pharmacology and use in clinical treatment are discussed.

The literature has been carefully reviewed and the book may be regarded as a dependable source of information with respect to digitalis and allied drugs. C. W.

MEDICINE IN INDUSTRY. By BERNHARD J. STERN, PH.D., Lecturer in Sociology, Columbia Univ.; Visiting Professor of Sociology, Yale University. Pp. 209; 15 tables. New York: Commonwealth Fund, 1946. Price, \$1.50.

THIS is one of the volumes issued under the auspices of the Committee on Medicine and the Changing Order of the New York Academy of Medicine, "as a contribution to contemporary thought on important questions in the general medical and health field." The author is well known as a writer upon topics which are closely allied to medicine and his selection by the committee assured a thoroughly documented and critical survey to demonstrate how perfectly this particular subject illustrates "the reciprocal effects of medicine and the technical, social, economic, and political changes that have taken place in American life."

Each of the 7 chapters represents a review of the subject under discussion both historically and currently. Appended to these chapters are references to all the important publications a student or practitioner is likely to need. The first 2 chapters, scientific developments and social and legislative backgrounds, take us from a papyrus of ancient Egypt to the most recently published laws enacted by various states up to last year.

Progress has been spotty. In all ages the need for reform has been recognized but it is only in recent years that there has been satisfactory achievement. Attainment of ideal conditions still depends on research, especially in the field of physiology. In considering the extent of industrial disability it is found that the data available do not approximate accuracy but that they are sufficient to permit an evaluation of the prevailing situation.

The study here of the handicapped worker in industry reveals a problem which the war

disabilities may help to solve by requiring a more constructive and enlightened policy on their employment than is now generally in force.

Preventive services which can be standardized, methods, and the extent of their utilization, are the result of intensive organization. It is now in the smaller plants that safety services are less available. There are compelling facts in the figures assembled under health programs and financial savings.

Medical care programs in industry are financed by employers and workers jointly, by workers alone or by employers alone. The review here of the current utilization of plans for health insurance in industry furnishes a perspective which can be used by individuals, groups of employers or communities for their own projects. Probably nowhere else can there be found a summary so well balanced.

The final chapter concerns the industrial physician; it states the conventional functions of those who are considered specialists. With the recognition of psychiatry as an aid in placement, avoidance of accidents and absenteeism, the alert industrial physician finds himself called upon to fulfil many other important functions. He will be a member of the safety committee, a consultant of management and probably personnel director. "The field of industrial medicine offers one of the most fruitful approaches to preventive medicine and public health. As the schools are agencies through which children can be reached *en masse* for the application of the most advanced findings of scientific medicine, so the factories, workshops and commercial establishments afford the opportunity to reach large aggregations of adult workers."

In an Appendix there is a tabulation of certain industrial prepayment medical plans. Organization of the oldest of these, the Hospital Department, Southern Pacific Company, dates back to 1867.

This small but important volume traces "the social, economic, legal, and professional setting within which industrial medicine has matured and the development of the scientific knowledge which has given industrial physicians increased competence to cope with diseases affected by occupations."

A. H.

PSYCHOLOGICAL MEDICINE. By DESMOND CURRAN, M.B., F.R.C.P., D.P.M., Psychiatrist and Lecturer in Psychological Medicine, St. George's Hospital, and Honorary Psychiatrist to the Midia Vale Hospital for Nervous Diseases, London; Temp. Surgeon Captain, R.N.V.R., and Consultant in Psychological Medicine to the Royal Navy; and ERIC GUTTMANN, M.D., M.R.C.P., Neuropsychiatric Specialist, Emergency Medical Service; formerly Research Psychiatrist, Nuffield Dept. of Surgery, Oxford; Psychiatrist to the Officer Board, National Fire Service. Foreword by J. J. CONYBEARE, M.C., D.M. (OXON.), F.R.C.P., Physician to Guy's Hospital, London. 2nd ed. Pp. 246; 20 ills. Baltimore: Williams & Wilkins, 1945. Price, \$3.50.

THE main changes and additions found in this issue are concerned with constitutional factors and psychopathic personalities, the affect and hysterical syndromes, and modern physical methods of treatment. Important chapters are: *Ætiology of Mental Disorder; Symptoms in Mental Disease; Psychiatric Case - Taking; Treatment; Constitutional Anomalies; Organic Syndromes; Psychiatric Aspects of Head Injury; Drug Addictions; Schizophrenia; The Affect Reaction Types; Obsessional States; Hysterical Reactions.* The appended *Psychiatry Associated With War Conditions* is enlarged.

Psychosomatic Medicine is now included with 4 distinct avenues of approach: The study of the psychologic origin of somatic symptoms and of organ neuroses; the discovery of psychologic factors precipitating or causing organic disease; somatic disease in relation to psychologic types; psychologic reactions to somatic disease and defect.

N. Y.

PROGRESS IN NEUROLOGY AND PSYCHIATRY.

Edited by E. A. SPIEGEL, M.D., Professor and Head of the Department of Experimental Neurology, Temple University School of Medicine. Fifty-three contributors. Pp. 708. New York: Grune & Stratton, 1946. Price, \$8.00.

IN this collaborate volume, the initial one in forthcoming annual reviews, the subject-matter is confined largely to the literature of 1945. Most space is given to Pharmacology of the Nervous System, where the

biography alone covers more than 23 pages; its chief concern is in diagnostic and therapeutic applications, with but little consideration of drug action mechanisms. Among other subjects at general and local anesthetics; the various aspects of alcoholic addiction, including the efforts of Alcoholics Anonymous and the Yale Plan Clinics; in the war neuroses, ergotamine tartrate has been employed in overcoming "sympathetic overactivity." In shock therapy, affective disorders respond much more readily than does the schizophrenic group. Electro-encephalograms show moderately severe "abnormalities" appearing in from 5 to 15% of the clinically "normal" control subjects. When penicillin is given alone, as yet there is no standardized method for its use in neurosyphilis. Under Group Psychotherapy, psychodrama receives careful consideration: on a specially designed stage, the subject is encouraged to act out his problems before an audience of patients, visitors and staff. There is a scarcity of summaries. This product of many collaborators is a timely book on opportune subjects, and its annual re-appearance doubtless will be looked forward to.

N. Y.

STUDIES IN HYPERTONY AND THE PREVENTION OF DISEASE.

By I. HARRIS, M.D., Honorary Director, Institute for Prevention of Disease, Honorary Physician, Liverpool Heart Hospital; in cooperation with J. T. IRELAND, B.Sc. (HONS.), A.I.C., Leverhulme Research Fellow, G. V. JAMES, M.Sc., A.I.C., Maurice Stern Research Fellow, EDWARD CRONIN LOWE, M.B.E., M.B., B.S., Director, Pathological Department, Southport Infirmary, Honorary Clinical Pathologist, Institute for Prevention of Disease, C. E. VERNON, M.Sc., A.I.C., Research Fellow. Pp. 114. Baltimore: Williams & Wilkins, 1946. Price, \$3.00.

THIS book is unusual. The introduction contains a bitter attack on the Medical Research Council, for adding calcium to the bread of wartime England, describing them as "dictatorship or priesthood . . . to hold their positions at all costs and by all means."

The author believes that emotional strain and diet are the cardinal factors in producing hypertony, or hypertension. Much original experimental and clinical data is presented

in sections dealing with calcium, cholesterol, protein intake, phosphorus and potassium. The author's discussions and conclusions are ingenious and thought provoking, but will not be accepted by all. The book is recommended primarily for students of hypertension and metabolic disease. J. G.

MANUAL OF TUBERCULOSIS. By E. ASHWORTH UNDERWOOD, M.A., B.Sc., M.D., D.P.H., Medical Officer of Health and Chief Administrative Tuberculosis Officer, County Borough of West Ham; Lecturer in the Royal College of Nursing; Fellow of the Royal Statistical Society. Pp. 524; 88 ills. Baltimore: Williams & Wilkins, 1945. Price, \$4.50.

SELDOM has the subject of tuberculosis been condensed as well as in this small volume by Dr. Ashworth Underwood. Within its pages the reader will find an informative and accurate account of the etiology, pathogenesis and evolution of tuberculosis, its institutional, medical and surgical treatment, the disease as it occurs in children, and the large problem of rehabilitation, as well as a very useful discussion of the administrative measures employed in tuberculosis control, the epidemiology of the disease and its public health aspects and its relation to social medicine. Quite appropriately, the book ends with a chapter on tuberculosis and war, in which a concise analysis is made on the basis of recent English experience of the impact of total war on a country previously well organized for tuberculosis control. The author is conservative in his account of tuberculosis, not leaning to any one of the several conflicting theories on pathogenesis, but giving a factual account of present understanding, and frankly admitting our ignorance of certain phases of the development of the disease.

The book is well written, and excellently illustrated. A useful feature is an accurate, comprehensive summarization at the end of each chapter. The volume is recommended for all persons interested in tuberculosis, and particularly for undergraduate and graduate medical students who wish a comprehensive view of tuberculosis for incorporation in their general understanding of medicine.

E. L.

PSYCHOTHERAPY IN GENERAL PRACTICE. Report on an Experimental Postgraduate Course. By GEDDES SMITH, Associate, The Commonwealth Fund. Pp. 38. New York: Commonwealth Fund, 1946. Price, 25c.

IN an experimental effort to determine if doctors could be "taught to practice in their own offices the kind of medicine psycho-neurotic patients need," 25 physicians in general practice attended a postgraduate course of 2 weeks duration at the University of Minnesota. As a course in psychotherapy, such complicated problems as deep-seated sexual dysfunction, were not attempted. From the results on 121 patients seen, it appears that a new outlook was given on medicine: "their attitude toward patients, their attitude toward disease, and their treatment of chronic illness." N. Y.

MEDICAL CLINICS OF NORTH AMERICA. July 1946. Mayo Clinic. Splenomegaly. Pp. 253. Philadelphia: Saunders, Price, \$16.00 yearly.

THIS is an informative and absorbing number. The leading article reviews well the disease entities to be considered should the examiner palpate the spleen in an adult patient. The papers on headache, gastroscopy, acute abdominal pain and chancroid stress the importance of the history in making the proper diagnosis. Physicians who have not had the opportunity to prescribe some of the more recently available chemotherapeutic agents will find the presentation on thiouracil, streptomycin, penicillin in the treatment of syphilis and the newer sulfonamides and antibiotics in intestinal diseases succinct and specific.

The reviews of the treatment of headache and habitual abortion, the present status of thiocyanates in hypertensive disease, the increasing abuse of sedative drugs and the use of various kinds of insulin critically cover the practical problems of managing such patients. Several of the clinics on the therapeutic agents present too enthusiastically the curative potentialities of these drugs. Studies on series of over 100 cases with a similar number of controls on placebo therapy are in the minority. An example is that more than a minority of patients with chancroidal ulcers do not get complete healing on sulfathiazole. Many patients having

acquired bacillary dysentery in this and other parts of the world are not improved by sulfadiazine even on near-toxic dosages. Increasing emphasis should be given to the toxic manifestations of these drugs which are so frequently prescribed.

The article on the Problem of Blackout and Unconsciousness in Aviators is unusual in a clinical presentation. This simple concise exposition of the vast amount of experimental work done in this field since 1939 is timely. It gives the medical man an opportunity to learn about the human problems in aviation relating to the survival of airmen, how the physiologic mechanisms were studied, what solutions were brought forth and what problems are still unanswered.

The physiologic investigation accomplished in the marvelous medical research program coordinated by the Office of Scientific Research and Development should be summarized in the future Clinics of the appropriate institutions.

J. H.

JEWISH LUMINARIES IN MEDICAL HISTORY.

By HARRY FRIEDENWALD, M.D., D.H.L. (Hon.), D.Sc. (Hon.), Professor Emeritus of Ophthalmology, University of Maryland, and a CATALOGUE of Works Bearing on the Subject of the Jews and Medicine From the Private Library of Harry Friedenwald. Pp. 199. Baltimore: Johns Hopkins Press, 1946. Price, \$3.00.

As indicated by the title, this volume consists of a brief discussion of Jewish luminaries in medical history, and a catalogue of

works bearing on the subject of the Jew in medicine, from the private library of the author.

If there is ever need for a source of information on the accomplishments of the Jew in medicine, the short lecture of Dr. Friedenwald, and what he calls, "A modest but unique collection . . . which in a measure illustrates the history of medicine among the Jews," supplies a basis for this purpose. This volume, well organized and written, but only sparingly illustrated, is a worthy addition to the library of any medical bibliophile. The value of the book is especially enhanced by the notes interpolated in the catalogue.

H. B.

PRINCIPLES OF HEMATOLOGY. By RUSSELL L. HADEN, M.A., M.D., Chief of the Medical Division of the Cleveland Clinic; formerly Professor of Experimental Medicine in the University of Kansas School of Medicine. Pp. 366; 167 ills. 3rd Ed. Philadelphia: Lea & Febiger, 1946. Price, \$5.00.

THIS indeed thoroughly revised 3rd edition of a valuable book written, as Dr. Haden says, "to simplify the studies of disorders of the blood for the student and physician," makes a very welcome third appearance. The description "of the technique of bone marrow puncture and the study of bone marrow films" that has been added increases materially the value of this excellent and advisedly "simple discussion of the fundamental principles of hematology." E. T.

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

MARCH, 1947

ORIGINAL ARTICLES

STUDIES ON MALIGNANT HEPATITIS

By GUNNAR ALSTED, M.D.

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IN recent years an increasing interest in hepatic diseases is manifest all over the world; this applies to both the acute and chronic forms. It is at least partly due to the violent outbreaks of infectious hepatitis observed during the war in many countries such as the epidemics among troops in the Middle East^{1,5,7,9} and in the Pacific,¹² in London,⁸ Italy and Malta.⁶ Moreover, interest is enhanced by the increased knowledge of the epidemiology and pathology of hepatic disorders, the latter of which is greatly aided by the basic investigations of Roholm and Iversen.¹³ The classic conceptions such as catarrhal jaundice and alcoholic cirrhosis have been widely, if reluctantly, discarded in favor of the classification as toxipathic and trophopathic disorders, according to Himsworth and Glynn.¹⁰ The former have toxic infectious causes, whereas the latter are due to some dietary deficiency. Thus the toxipathic disorders of the liver comprise all acute and many chronic forms of hepatitis, whereas the remaining forms of chronic hepatitis and cirrhosis must be regarded as trophopathic, and this applies presumably also to the alcoholic cirrhosis.

In Denmark, acute hepatitis has run a course parallel to that in the rest of the world. As shown in Table 1 an increased number of cases has been observed during

the last 3 or 4 years, the disease being 7 to 8 times as frequent as usual.

TABLE 1.—REPORTED CASE INCIDENCE OF
HEPATITIS IN DENMARK

	Entire country	Dept. B
1935	5,347	31
1936	2,761	21
1937	2,208	23
1938	2,257	25
1939	2,718	16
1940	3,079	19
1941	6,461	35
1942	10,819	36
1943	18,008	30
1944	15,977	46
1945	14,184	85

The increasing frequency has, as might be expected, reflected itself in most of the medical hospital departments over the country. An example of this can be seen in Table 1, where there is also given the total number of cases of acute and chronic hepatitis, treated in Medical Dept. B of Frederiksberg Hospital in the period 1935-1945. The explanation of the marked increase of acute hepatitis in a country like Denmark, however, still remains to be determined.

In Dept. B, however, it soon became evident that besides the increasing frequency of acute hepatitis, another problem presented itself—a problem of vital importance because of its seriousness and unusualness. Acute hepatitis tends to

run a benign course, terminating usually within a shorter or longer time in complete recovery. Now and then, however, a few cases are recorded which run either an acute lethal course or terminate in cirrhosis. Some of our cases developed differently. In 1944 and 1945 a considerable number of cases, instead of running the usual benign course, had a very protracted course. Many of these patients developed edema and ascites and death occurred in half of them. It was still more striking that this malignant hepatitis occurred almost exclusively in women over 45 years of age in contrast to acute infectious hepatitis, which ordinarily is most frequent in young men and women.

Malignant hepatitis is no isolated phenomenon. Björneboe and Bröchner-Mortensen⁴ and Jersild¹¹ have published similar observations from the Municipal Hospital, Copenhagen and Bispebjerg Hospital, Copenhagen, but I am not aware of reports from countries other than Denmark.* Bergstrand,² however, in 1930, reported 150 similar cases, of which 97 occurred in Sweden in 1927. There are, however, essential differences between Bergstrand's cases and the disease as it appears in Copenhagen today. Among his 97 cases, 28% were male, and 36 of the cases occurred in persons under 40. On the other hand, the clinical course and pathology closely resemble that observed in Copenhagen during the 2 to 3 last years,

Because of the frequent incidence of malignant hepatitis, its serious and protracted course, and its high fatality rate, the following problems presented themselves: (1) Is the incidence of malignant hepatitis an outcome of the highly increased frequency of infectious hepatitis, *i. e.*, are cases of malignant hepatitis just severe cases of ordinary acute infectious hepatitis, or is this a new disease essentially different from acute hepatitis? (2) Is it possible at an early stage to establish a differential diagnosis between benign and

malignant hepatitis? An answer to these questions is the primary object of the present studies.

FREQUENCY AND SEX INCIDENCE IN MALIGNANT HEPATITIS. As mentioned above the first cases of malignant hepatitis were observed in 1944. Consequently, I have collected and studied all cases of hepatitis and cirrhosis, treated in Dept B in the period of Jan. 1, 1944, to March 31, 1946. The relatively few cases of Laennec cirrhosis with an alcoholic etiology have been eliminated and the same applies to biliary and syphilitic cirrhosis (*hepar lobatum*) and "cirrhose cardiaque." This leaves 136 cases of which 27 were fatal. Postmortem examinations were performed in 24 cases. The incidence of the cases appears in Table 2.

TABLE 2.—HEPATITIS IN DEPT. B.
Jan. 1, 1944, to Mar. 31, 1946

	Men	Women	Total
Benign	41	41	82
Malignant:			
Surviving . . .	0	27	27
Fatal	3	24	27
Total	44	92	136

The table shows that while the benign cases have had an equal sex distribution, the malignant cases have shown a marked female predominance and a fatality rate of 50%. Clinical criteria for the diagnosis of malignant hepatitis have been lethal exitus, development of portal stasis, or a clinical course of 4 months duration or more.

AGE DISTRIBUTION. The age distribution of the hepatitis patients appears in Tables 3 and 4.

The benign cases are put down in Table 3 and the malignant ones in Table 4. From these 2 tables it appears that benign hepatitis is most frequent in younger persons, and this is most marked in males where 38 of 41 men (93%) are under 45 years of age, while only 27 of 41 women (66%) are in the same age groups. Ordinarily the disease is still more frequent in chil-

* Since our receipt of this report, Baldwin Lucké and Tracy Mallory have reported (*Am. J. Path.* 22, 867, 1946) on 196 cases of fatal hepatitis in the U. S. Army of which 53% were of a fulminating type.
—EDITORS.

dren under 15 years of age, but this is not manifest in our material data as Dept. B only admits a limited number of children.

TABLE 3.—AGE DISTRIBUTION IN BENIGN HEPATITIS

Years	Men	Women	Total
0-14	3	2	5
15-24	11	11	22
25-34	22	10	32
35-44	2	4	6
45-54	2	8	10
55-64	1	2	3
65-74	0	3	3
75-84	0	1	1
85 and over	0	0	0
Total	41	41	82

The age distribution in benign hepatitis is in striking contrast to the age distribution in malignant hepatitis. In the latter disease only 3 of 51 women (6%) are under 45 years of age, all of the 3 men being over 45 years of age. The numbers in brackets indicate fatal cases, averaging 50%. The fatality rate appears to increase with age.

TABLE 4.—AGE DISTRIBUTION IN MALIGNANT HEPATITIS

Years	Men	Women	Total
0-14	0	0	0
15-24	0	0	0
25-34	0	2 (0)	2 (0)
35-44	0	1 (0)	1 (0)
45-54	0	14 (7)	14 (7)
55-64	1 (1)	13 (5)	14 (6)
65-74	2 (2)	16 (9)	18 (11)
75-84	0	4 (3)	4 (3)
85 and over	0	1 (0)	1 (0)
Total	3 (3)	51 (24)	54 (27)

(Numbers in brackets are fatal cases)

LIVER FUNCTION TESTS. To obtain information about prognosis the results of various liver function tests performed on patients in both groups are being compared. In Dept. B few liver function tests are in use. On the other hand they have been repeatedly performed in all patients, because in our view it is preferable to apply few but familiar tests, the results of which can be reasonably well estimated, rather than to apply a greater number more or less at random. Beside the ordinary urinary tests, ieterus index, Takata's reaction, Bauer's galactose test

and determination of serum iron have been carried out repeatedly in all of these patients. The 3 blood tests mentioned have the advantage that they can be carried out on the same blood sample. The results are presented as follows: (1) immediately after admission, (2) the highest values observed during the clinical course and (3) the results before discharge or lethal exitus. It has not been possible to do this in all fatal cases as some of the patients died shortly after admission. In these cases a single group of tests only is given. In other patients the poor condition made the tests extremely difficult to obtain.

TABLE 5.—ICTERUS INDEX IN HEPATITIS

	Positive		Negative	
	No.	%	No.	%
A. Benign cases:				
41 male:				
On admission . . .	38	93	3	7
During illness . . .	38	93	3	7
On discharge . . .	0		41	100
41 female:				
On admission . . .	34	83	7	17
During illness . . .	36	88	5	12
On discharge . . .	2	5	39	95
B. Malignant cases:				
27 surviving:				
On admission . . .	26	96	1	4
During illness . . .	27	100	0	
On discharge . . .	14	52	13	48
27 fatal:				
Before death . . .	24	89	3	11

Icterus Index. In Table 5 the ieterus index, according to the method of Meulengraecht has been put down as positive or negative. Positive means an index of 15 or over. A high limit has intentionally been chosen to eliminate unequivocal results. The benign cases are subdivided into male and female cases while the malignant ones are subdivided into surviving and fatal cases. This arrangement is followed in the subsequent tables.

As appears from the table, about 90% of the benign cases had an ieterus index of 15 or over on admission, or during the course of the disease. All patients, 2 women excepted, were discharged without jaundice. There was no difference between men and women. Those 10% or so of the patients who were not jaundiced

in hospital had been jaundiced at home prior to admission.

All surviving patients with malignant hepatitis were jaundiced on admission, or became jaundiced during the course of the illness. Half of them were still jaundiced on discharge, that is to say after a stay in hospital of several months duration. Of the 27 fatal cases, 3 were not jaundiced in hospital but had been on an earlier stage.

Accordingly, the icterus index provides no reliable informations with the exception that protracted jaundice is ominous, just as might be expected. A normal icterus index does not, on the other hand, guarantee against malignant hepatitis, as is evident from the 3 fatal non-jaundice cases.

TABLE 6.—TAKATA'S TEST IN HEPATITIS

	Positive		Negative	
	No.	%	No.	%
A. Benign cases:				
Male:				
36 on admission	3	8	33	92
14 during illness	1	7	13	93
20 on discharge	0		20	100
Female:				
33 on admission	4	12	29	88
17 during illness	1	6	16	94
24 on discharge	1	4	23	96
B. Malignant cases:				
Surviving:				
27 on admission	19	70	8	30
26 during illness	24	92	2	8
27 on discharge	18	67	9	33
Fatal:				
19 on admission	14	74	5	26
16 before death	14	87	2	13

Takata's Test. In Table 6 the results of Takata's test are recorded. Positive reaction means medium precipitation in at least 3 tubes, corresponding to the reaction generally indicated as $++$. It will be observed that while Takata's test was negative in 90% of the benign cases on admission and, furthermore, became negative in all remaining benign cases, 1 case excepted, it was positive in from 70 to 74% of the malignant cases on admission. In the course of the disease 92% of the surviving patients with malignant hepatitis developed a positive Takata test, and it remained positive in 67% of these patients on discharge. In 16 pa-

tients Takata's test was carried out shortly before death; it was positive in 14 (87%). Takata's test indicates an abnormal albumin/globulin ratio in the plasma. In hepatitis this is due to a decreased albumin formation in the liver.

The data in Table 6 perhaps establishes the great differential diagnostic and prognostic value of Takata's test in hepatitis. As long as it remains negative a benign course is most likely, *ceteris paribus*. The reverse is still more pronounced; if the test becomes positive, and, especially, if it remains positive the case is probably a malignant one.

TABLE 7.—BAUER'S GALACTOSE TEST IN HEPATITIS

	Positive		Negative	
	No.	%	No.	%
A. Benign cases:				
Male:				
41 on admission	20	49	21	51
13 during illness	6	46	7	54
24 on discharge	12	50	12	50
Female:				
46 on admission	28	70	12	30
19 during illness	12	63	7	37
30 on admission	13	43	17	57
B. Malignant cases:				
Surviving:				
26 on admission	17	65	9	35
26 during illness	23	88	3	12
26 on discharge	19	73	7	27
Fatal:				
16 on admission	11	69	5	31
7 during illness	7	100	0	
9 before death	6	67	3	33

Bauer's Galactose Test. The results of the galactose tests are demonstrated in Table 7. The test has been regarded as positive when there has been a urinary excretion of 3 gm. of galactose. It is seen in the table that the test has been positive in half of the benign cases or so, and this percentage has remained practically unchanged during the disease even when all of the remaining clinical symptoms have disappeared.

In malignant cases a positive galactose test was somewhat more frequent, in almost 70% of the cases. During the further course of the disease it became positive in practically all cases, later again becoming negative in some cases, among

these even lethal ones. In many malignant cases there was a strikingly positive reaction with an excretion of more than 10 gm. of galactose. Apart from this inconstant finding the galactose test does not give any prognostic help worth mentioning. In cases where it runs a course parallel to Takata's test, it may eventually give some further support to the estimation of the character of the case. It is extraordinary to notice the frequent incidence of a positive galactose test in the malignant cases, the test, in my opinion, most usually being negative in the ordinary atrophic cirrhosis of Lacnnc.

Serum Iron. Determination of serum iron has been used for several years in Dept. B as a help in the differential diagnosis between hepatitis and obstructive jaundice. According to Bjerre and Christoffersen,³ an elevation of the serum iron to 200 μ g. per 100 ml. and over is observed in 70% of all cases of acute hepatitis, while normal or slightly lowered values are obtained in obstructive jaundice.

TABLE 8.—SERUM IRON IN HEPATITIS

	Positive		Negative	
	No.	%	No.	%
A. Benign cases:				
Male:				
40 on admission	7	18	33	82
31 during illness	16	52	15	48
34 on discharge	5	15	29	85
Female:				
38 on admission	8	21	30	79
27 during illness	11	41	16	59
35 on discharge	1	3	34	97
B. Malignant cases:				
Surviving:				
27 on admission	4	15	23	85
27 during illness	14	52	13	48
27 on discharge	1	4	26	96
Fatal:				
16 on admission	3	19	13	81
10 during illness		0	10	100
14 before death		0	14	100

In Table 8 are given the serum iron determinations in our cases. It appears that both in benign and malignant hepatitis a serum iron of more than 200 μ g. per 100 ml. is found in half of the patients. In benign cases it later decreases, as a rule, somewhat more slowly than the icterus index, but in 10% of the patients it

remains elevated above 200 μ g. per ml. on discharge. In malignant cases the serum iron runs a similar course. It may be significant that normal values were obtained in all of the 14 patients examined immediately before death. It has to be admitted, however, that no great prognostic help is given by determination of serum iron in the malignant cases. At the very best one may get a slight indication, supporting or weakening a diagnosis based on other facts.

CLINICAL SYMPTOMS. *Ascites.* Development of ascites and edema must, as a matter of fact, be regarded as a very serious sign, provoked as it is partly by cirrhotic processes in the liver and partly by a lowered osmotic pressure in the plasma, due to deficient albumin formation in the liver.

TABLE 9.—ASCITES IN HEPATITIS

	Positive	Negative
A. Benign cases:		
52 male and female	0	82
B. Malignant cases:		
27 surviving:		
On admission	2	25
During illness	5	22
On discharge	2	25
Fatal:		
24 on admission	11	13
23 during illness	19	4
27 before death	20	7

In Table 9, the incidence of clinically demonstrable ascites in all of the patients is given. While ascites developed in none of the benign cases it was found on admission in 2 of the surviving malignant cases. In 3 of these cases considerable ascites developed during the illness, accompanied by pronounced edema of the legs. In all 3 patients, 2 younger and 1 older woman, however, ascites and edema disappeared little by little during some months as complete clinical recovery was observed and all function tests became normal. Thus a symptom as serious even as ascites must be estimated with reservation as to prognosis. That portal stasis still is extremely serious is sufficiently evident from the development in the fatal cases. On admission, ascites was found in 11 of

24 cases but at the time of death it was present in 20 of 27 patients.

Pain. In our few cases of malignant hepatitis a striking symptom was pain. Several of these patients suffered from repeated attacks of intense pain under the right costal margin. At first when the disease was new and unknown the diagnosis of gall stones was often made, and 2 of these patients had laparotomies performed. It is my impression that pain prevails chiefly in the early stages of the disease and that it is often accompanied by fever. In many malignant cases, however, pain never occurs. On the other hand, patients with infectious hepatitis not infrequently give a history of pain, as it is well known. In Table 10 is shown the incidence of pain in our material.

TABLE 10.—PAIN IN HEPATITIS

	Positive		Negative	
	No.	%	No.	%
A. Benign cases:				
41 male	12	29	29	71
41 female	7	17	34	83
B. Malignant cases:				
27 surviving	18	67	9	33
27 fatal	10	37	17	63

As will be seen, 23% of the benign cases give a history of pain. In the surviving malignant cases the corresponding number is 67% and in the fatal cases 37%. A numerical setting up of a symptom-like pain must always, however, be estimated with a certain reservation. As to pain its importance depends on its nature rather than on its frequency. In most of the benign cases the pain has manifested itself as a slight diffuse oppression in the abdomen. In malignant cases the pain

most often occurs as attacks of intense ache, localized under the right curvature. Such attacks favor, if gall stones can be excluded, the diagnosis of malignant hepatitis. In this disease, however, pain is of no special serious prognostic importance, being more frequent in surviving than in fatal cases.

Blood. A symptom of frequent occurrence in hepatic cirrhosis is macrocytic anemia. As it might be possible to distinguish between benign and malignant hepatitis through differences in the blood pictures, red cell counts were done in 8 patients with benign hepatitis and in 13 surviving and 10 fatal cases of malignant hepatitis. All counts were performed on women. The mean results are to be found in Table 11.

TABLE 11.—MEAN BLOOD COUNTS

	Hemo- globin	R.B.C.	C.I.
A. Benign cases:			
8 female	88%	4 03	1.08
B. Malignant cases:			
13 surviving	76%	3.57	1.07
10 fatal	75%	3 41	1.10

It will be seen that the counts are somewhat lower in the malignant cases than in the benign ones. This was to be expected according to the age distribution of the disease. The difference, however, is so slight that it can hardly yield any diagnostic or prognostic help.

DURATION. The duration of the disease is shown in Table 12. The pre-icteric symptoms in hepatitis being rather vague and non-characteristic, the onset of the disease has been counted from the development of jaundice, this symptom being

TABLE 12.—DURATION OF SYMPTOMS (IN MONTHS)

	Less than 1	1	2	3	4	6	7	8	9	10	11	12 and over	Total
A. Benign cases:													
Male	15	18	5	3									41
Female	12	21	6	2									41
Total	27	39	11	5									82
B. Malignant cases:													
Fatal	1	2	4	5	3	3	0	1	1	1	0	3	27
Stationary	0	0	1	0	0	1	0	1	1	3	0	2	10
Improved or cured	0	0	0	1	6	0	1	4	1	0	1	3	17
Total	1	2	5	6	9	4	4	5	3	5	0	8	54

so conspicuous that it will hardly be overlooked long. The duration has in benign cases been counted until full clinical recovery, in malignant cases until death or discharge without regard to whether the discharge has taken place at full clinical recovery, considerable or only slight improvement or stationary condition during a longer period.

From the data it appears that the duration in most of the benign cases is less than 2 months and in the remaining ones 3 to 4 months. In a considerable number of cases, malignant hepatitis runs an acute course; thus no less than 12 of 54 patients died in less than 4 months. In most of the cases the duration was 4 to 9 months, only 8 lasting more than 1 year. These facts rather than the pathologic changes justify the term malignant hepatitis which must be preferred to the term chronic hepatitis even if many of the cases run a decidedly chronic course.

PATHOLOGIC ANATOMY. In 24 cases (3 male and 21 female) of a total of 27 fatal cases postmortems have been carried out. The pathologic findings have been strikingly uniform. It is remarkable how

slightly the varying duration has influenced the pathologic changes. Macroscopically, the liver is extremely reduced in size, often being only half or two-thirds of its normal size. The form is unchanged in its broad features, the edges sharp. The consistency is tough, rather compact and yet flaccid. The surface shows an irregular finer or more coarse ruggedness and granulation, bigger and smaller roundish, smooth, bulging, yellowish or yellow-greenish areas, strongly contrasting with intervening darker, gray-red or gray-green, sunken, wrinkled areas, frequently of considerable extent. The cut surface exhibits a corresponding picture of slightly prominent, softer, dull, yellowish-green, yellowish islands of liver tissue, irregularly distributed in a cicatrized connective tissue which is sunken, smooth, more compact, grayish or red-grayish.

Microscopically, the prominent areas consist of islands of liver tissue, the cells of which show all stages of transition from apparently normal, newly formed cells, through turgid, granular and fatty degenerated cells to completely necrotic cells. Bile pigment lies free between or in the



FIG. 1

FIG. 2

FIG. 1.—Section of liver showing liver cell islands surrounded by cicatrized connective tissue.
FIG. 2.—Same section as Figure 1, at higher magnification, showing degeneration of liver cells and lymphocyte infiltration.

cells, lobular delimitation is poor. In places where the tissue is best preserved necrosis and degeneration frequently seem to be most pronounced in the centers of the lobules. The outer zone, however, is often destroyed and lobules are dispersed in isolated bigger and smaller roundish groups of cells. The shrunken tissue between the islands of liver tissue consists of fibrous cicatrized tissue, containing varying numbers of capillaries with an increased number of leukocytes. Furthermore, there are numerous proliferated bile ducts with dark staining low cells, and here and there isolated liver cells or small groups and areas of these. The tissue is conspicuously infiltrated with lymphocytes, a few plasma cells, migrant cells and nuclear remnants, as well as scattered leukocytes. In the original portobiliary spaces the round cell infiltration assumes an almost follicular character.

As a whole, the picture conveys the impression of a continuous degenerative process, developing into necrosis with subsequent organization of the necrotic liver tissue and cicatrization, combined with endeavors of regeneration from the liver tissue and continued degeneration of the newly formed liver tissue.

The pathologic changes described here are characteristic of malignant hepatitis and distinctly different from those observed both in acute hepatitis and acute yellow atrophy. They are in close accordance with those reported by Bergstrand. Whether the changes in the initial stages of malignant hepatitis are characteristic of this disorder or correspond to those observed in acute hepatitis cannot be determined from this material, as no liver biopsies have been performed. Maybe the latter possibility is more likely, even if it is striking that in acute fatal cases changes were found, closely resembling those described above.

Likewise, the absence of liver biopsies

prevents the information whether the pathologic changes decrease and disappear in patients with malignant hepatitis where clinical recovery is complete. This, of course, is a great lack, but we did not feel justified in exposing these patients with their small flaccid livers to the trauma of repeated liver biopsies.

ETIOLOGY. Infectious hepatitis is generally regarded as an infectious disease, caused by a filterable virus. Is malignant hepatitis just a variety of this disease, provoked by special factors, or is it a separate disease, perhaps not even an infectious one? It is difficult to answer the question at present. In its early stages the disease can hardly be distinguished from benign hepatitis but this does not prove that it is the same disease. Acute hepatitis and serum jaundice, for instance, are regarded as separate diseases because of their different time of incubation, in spite of their otherwise uniform course and uniform pathologic changes.*

Trying to find out whether in this material difference between the etiology in benign and malignant hepatitis can be traced, I have in Table 13 put down evidence that might be of etiologic importance.

TABLE 13.—ETIOLOGIC FACTORS

	Benign cases		Malignant cases	
	Male	Female	Surviving	Fatal
None	28	29	25	27
Contagion	11	3	1	0
Arsenic therapy	0	3	0	0
Syphilis	1	1	0	0
Pregnancy	0	2	1	0
Diabetes	1	3	0	0
Total	41	41	27	27

Table 13 shows that in 25 of 82 benign cases etiologically significant facts were found, 14 being cases with proved contact with patients suffering from hepatitis. In only 2 of 54 malignant cases could etiologic facts be traced. The numbers are small but even so the difference seems to be too big to be entirely casual; it rather

* Recent studies in the United States have given evidence that the viral etiologic agents of acute (infectious) hepatitis and homologous serum hepatitis are not identical and differ at least in their antigenic properties.—EDITORS.

suggests an etiology in malignant hepatitis different from the one in benign cases.

There is, however, another fact which still more corroborates this suggestion.

In Table 14 will be seen the total number of cases of acute infectious hepatitis in Denmark in the period 1935-45, subdivided for children, men and women. Furthermore the corresponding total number of deaths from acute and chronic hepatitis and cirrhosis is included. It is significant that while the increase of acute hepatitis since 1941 is most marked in children and men, the marked increased number of deaths in 1944 and 1945 only concerns the women, giving in 1945 a

that is not so, neither in Dept. B nor in the entire country. As shown, the malignant form occurs practically only in women over 45 years of age, whereas the benign form is predominant in children and young men and women with a slight male predominance. This is in perfect accord with the conditions in Dept. B. Because of this fact and the etiologic differences suggested above, it seems thus far to be justifiable to maintain that acute infectious hepatitis and malignant hepatitis are 2 separate disorders. The former is of varying frequency, at times it is epidemic, and it is always predominant in young persons with an almost equal sex

TABLE 14.—CASES OF INFECTIOUS HEPATITIS IN DENMARK 1935-45 AND DEATHS FROM HEPATITIS AND CIRRHOSIS IN THE SAME PERIOD

	Hepatitis			Deaths from hepatitis and cirrhosis					
	Children	Men	Women	Children	Men		Women		
					No.	%	No.	%	
1935	3010	1221	1116	3	47	3.8	35	3.1	
1936	1309	760	692	1	52	6.8	30	4.0	
1937	975	607	626	2	54	8.9	18	2.9	
1938	911	687	659	2	54	7.9	25	3.6	
1939	1307	687	724	1	63	9.2	19	2.6	
1940	1471	813	795	0	36	4.4	17	2.1	
1941	2879	1854	1728	2	52	2.8	43	2.5	
1942	4810	3310	2699	1	59	1.8	24	0.9	
1943	7670	5605	4732	3	47	0.8	40	0.8	
1944	6198	5249	4530	3	57	1.1	116	2.5	
1945	4170	5376	4638	6	91	1.7	534	11.5	

fatality rate of 11.5% of the total number of cases of hepatitis, while the male fatality rate is much lower than previously noted. This can, as far as I can see, only be explained by assuming that the greater part of the male deaths is due to the ordinary cirrhosis of Laennec, always a disease predominant in men, the incidence of which has remained unchanged in the last years, unaffected by the variations in the frequency of hepatitis. The great increase of female deaths must, however, be ascribed to malignant hepatitis, the conditions in the whole country thus corresponding exactly to those in Copenhagen.

If malignant hepatitis were nothing but a variety of acute infectious hepatitis, a distribution of the malignant cases might be expected that was in accordance with the distribution of the acute cases, but

distribution. It is usually benign in its course, this also being the case in the recent epidemic outbreaks mentioned before. The latter has not been observed before 1944 and it occurs practically only in elderly women. It runs an extremely malignant course, having a fatality rate of 50%.

But even if malignant hepatitis is conceived as a separate entity, no explanation of its etiology has yet been given. It is not even known whether it is an infectious disease. Contagiousness has not been definitely proved and transmission experiments do not appear tempting with a disease of this nature. No other certain etiology has been substantiated. Gold and arsenic therapy and alcohol may decrease resistance against acute hepatitis⁶ but these facts are absent in the material investigated here. The only features ap-

parently in common are the age and sex, 50 of 54 patients being climacteric or post-climacteric women. Only 1 woman is less than 35 years of age, the remaining 3 patients being elderly men. Obviously hormonal factors must be considered in the etiology but any particular information concerning this point cannot be obtained from the material presented here.

Repeated and complicated pregnancies might play a part in the later development of malignant hepatitis in these elderly women.

TABLE 15.—PREGNANCIES IN FEMALE CASES OF MALIGNANT HEPATITIS

Pregnancies	Surviving	Fatal
0 15	68%	4 27%
1 4	32%	5
2 1		3
3 1		2
4 1		1
	22	15
No information 5		9
	27	24

Table 15 gives the number of pregnancies in the female cases of malignant hepatitis as far as information has been available. The numbers are too small to be significant. They do seem to imply, however, that no more pregnancies have occurred among these women than among women in average. The reverse appears to be the case: the number of unmarried women being comparatively large. As to pregnancy no comparison can be made between benign and malignant hepatitis because of the different age distribution of the diseases.

All theories on the etiology in malignant hepatitis must therefore remain speculative. Demands on the liver caused by various vaccinations, so frequent in recent years, may play an etiologic rôle. It is difficult to understand, however, why this feature should be predominant in elderly women who would hardly be more frequently vaccinated than the remaining part of the population.

TREATMENT. The treatment in malignant hepatitis must be considered just as uncertain as the etiology. The treatment

substantially is symptomatic, the chief principle being to do no damage. In Dept. B the patients have been given a balanced light diet with the addition of vitamins and symptomatic treatment as needed. Rest in bed has been considered the chief curative measure, the patients having been kept in bed until the disappearance of clinical symptoms or until the condition has remained stationary over a longer period.

Theoretically, an early treatment with methionine, cystine, choline or, eventually, estrin should be indicated. The treatment should begin at an early stage when the pathologic changes in the liver have only slightly developed, as it is difficult to imagine how any drug therapy should be able to influence pathologic changes of the character described above. Before it is possible to establish an early differential diagnosis between benign and malignant hepatitis it will, however, be extremely difficult if not impossible to estimate the therapeutic results, as all cases responding to treatment would, eventually, be conceived as benign cases.

Conclusion and Summary. One may conclude from the observations reported here that an extremely malignant form of hepatitis has been appearing in Denmark since 1944. It is predominant in women over 45 years of age and has a fatality rate of 50%. Most frequently its duration is from 4 to 9 months, but both a much more acute and a more protracted course may be observed. The clinical features are jaundice, frequent febrile attacks of pain and development of symptoms of portal stasis. As to prognosis, the result of Takata's test is important, whereas the remaining liver function tests applied are of secondary value only. The lesions are characterized by destruction of the liver tissue, and in the more chronic cases development of a cicatrized connective tissue. Therefore, the etiology is obscure. Both etiologically and clinically the disease differs in essential points from acute infectious hepatitis. The treatment has until now been entirely symptomatic.

Not wishing to delay this important article by communicating with the author in Denmark, we venture to suggest a different interpretation from that given above; namely, that the increased incidence in both sexes may be due to the spread of the virus of epidemic hepatitis in sufficiently benign form to lower the mortality rate in both sexes, though, for reasons still unknown, the mortality rate in 1944 and 1945 is much higher in women than in men.—EDITORS.

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DIAGNOSIS OF ACUTE RESPIRATORY TRACT INFECTIONS*

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DURING the past several years we have had an opportunity to study patients with acute respiratory tract infections, particularly those with primary atypical pneumonia, and the results of certain investigations have been published.^{1,5} During the course of the study patients were admitted to this hospital who were thought to have primary atypical pneumonia. Following careful examination some of the patients seemed clearly to have respiratory infections of another sort, and in others revision of the initial diagnosis was made necessary by subsequent laboratory findings. The results of studies on these patients serve to call attention to the difficulties of accurate clinical diagnosis of acute respiratory infections. It is the purpose of this communication to emphasize these difficulties, to assess the extent to which laboratory studies may serve to establish accurate diagnoses in such conditions, and to present evidence indicating that more than one infectious agent may be operative in some instances of acute respiratory infection. For the purposes of this study the attitude was adopted that all final diagnoses were to depend upon positive laboratory evidence. In those instances in which only negative laboratory data were obtained, a specific final diagnosis was not assigned.

Patients and Methods. *Patients.* The 26 patients included in this report are made up of 2 small groups, each admitted to the Hospital of The Rockefeller Institute during

mild influenza epidemics in the New York area, 1 in the winter of 1943-44 (influenza A) and the other in the winter of 1945-46 (influenza B). In each group patients are included who were admitted between the first and last cases showing evidence of influenza virus infection. The patients are few in number, all but 1 were in military service, and they were young, previously healthy adults. These facts, which might be regarded as objectionable were an attempt made to draw general inferences from the groups, obviously do not weigh against consideration of each patient as an individual diagnostic problem.

Procedure. On admission, after a history was obtained, each patient was examined. Roentgen rays of the chest were taken, swabbings of the nasopharynx were obtained, and blood was drawn for culture as well as for hematologic and serologic studies. Sputum was collected when available. Nasopharyngeal washings were collected from selected patients. Some of these procedures were repeated at weekly or more frequent intervals.

Bacteriologic Procedures. Swabbings of the nose and throat were streaked on rabbit blood agar plates. Sputum was similarly cultured. Either a small amount of sputum or the throat swab was also cultured in a selective medium to facilitate the isolation of certain non-hemolytic streptococci.⁵ Sputum, or a portion of the throat washings, was inoculated intraperitoneally in a mouse. A stained smear of the sputum was made, and if it showed organisms resembling pneumococcus, an attempt was made to identify this organism by the direct "quellung" technique.

* The Bureau of Medicine and Surgery does not necessarily undertake to endorse the views or opinions which are expressed in this paper.

In the identification of organisms recovered by these methods, various procedures were employed. Certain common nose and throat organisms were identified by their colony characteristics and appearance on stained smears; these included the staphylococci, organisms of the *Neisseria* group, *Hemophilus hemolyticus* and diphtheroids. Organisms resembling beta-hemolytic streptococcus, pneumococcus or *Hemophilus influenzae* were further identified. Those suspected of being beta-hemolytic streptococci were subcultured, extracted, and the extracts set up against diagnostic serum for each Lancefield group; organisms belonging to Group A were typed by the Lancefield precipitin technique. Strains of pneumococcus were identified by the "quellung" method, employing sera for Types I through XLIII. Organisms resembling *H. influenzae* were routinely tested by the "quellung" method using typing sera A through F. Non-hemolytic streptococci recovered in the selective medium were grown on 5% sucrose agar, to distinguish *Str. salivarius* from the organism known as streptococcus MG,⁵ and further identified by the "quellung" technique with antistreptococcus MG serum.

Influenza Virus Identification. Strains of influenza virus were recovered by the inoculation of throat washings into the amniotic sac of the chick embryo. The presence of virus in embryonic fluids was recognized by chicken erythrocyte agglutination, and the virus was identified by the inhibition of this effect with specific antisera against influenza A or B virus.

Serologic Procedures. Standard methods were employed in testing the sera for pneumococcus agglutinins, streptococcus MG agglutinins,⁵ cold hemagglutinins,⁴ influenza virus antibodies,² and antistreptolysin O.⁶ The antistreptolysin O tests were done through the courtesy of Dr. Sidney Rothbard of the Hospital of The Rockefeller Institute.

LABORATORY STUDIES, RESULTS AND INTERPRETATION. The patients included in this study are listed in Table 1 in the order of their admission. Their initial diagnoses, laboratory findings, and final diagnoses are shown. Since one purpose was to relate laboratory data to the clinical picture, the laboratory findings and the serologic tests employed, as well as

the criteria for their evaluation will be discussed. The relation of the initial diagnosis to the final diagnosis will be considered later.

1. *Pneumococcus.* As shown in Table 1, pneumococcus was recovered from 12 patients. Types 4, 7 (Case 14), 19 and 28 were typed directly in the sputum. Type 7 (Case 25) grew in pure culture from nasal swabs. Type 43 was obtained from nose and throat cultures. Types 3, 6, 8, 13, 15 and 34 were recovered only after mouse inoculation, and could not be identified in nose, throat or sputum cultures.

Acute and convalescent sera from each patient from whom pneumococcus was recovered were tested for the presence of agglutinins against the homologous type. The results are to be seen in Table 1. Agglutinins were present in none of the acute sera in a dilution of 1:10. Agglutinins in low titer developed in the convalescent sera of both patients with Type 7 (Cases 14 and 25) and in the serum of the patient with Type 8 (Case 26). The reason for the failure to identify pneumococcus directly in the sputum of Case 26 and in Case 25 was probably attributable to previous treatment, in 1 case with sulfadiazine, in the other with penicillin. Case 16 failed to develop demonstrable agglutinins against Type 4, but mouse protective antibody was present in serum obtained on the 8th day and attained high titer later. The course and serologic findings warrant a diagnosis of pneumococcal pneumonia in Cases 14, 16, 25 and 26.

No positive evidence was obtained regarding the rôle of pneumococci in the patients with bronchitis but without pneumonia. The direct identification of Type 28, in the sputum of Case 23, is of doubtful significance; this patient developed significant titers of both cold hemagglutinins and streptococcus MG agglutinins.

2. *Beta-hemolytic Streptococcus.* Beta-hemolytic streptococci were recovered from the nose, throat or sputum of 8 patients. One organism (Case 20) belonged to Group B and another (Case 12) to Group G; the remainder were Group A.

In 4 instances (Cases 1, 17, 19, 21) the streptococci were present in large numbers; in 2 (Cases 23 and 24) only a few colonies were seen. The streptococci from Cases 1, 19 and 23 were not typable, Cases 21 and 24 both had Type 3, and Case 17 Type 17.

Acute and convalescent sera from each patient with a Group A streptococcus were tested for antistreptolysin O content. In this test the degree to which serum inhibits hemolysis of erythrocytes by streptolysin O, derived from Group A beta-hemolytic streptococcus, is measured. The antistreptolysin titers of sera from these patients are recorded in Table 1. Evidence of infection by Group A organisms rests not upon the titer of a single serum, but upon the *increase* in antistreptolysin titer during convalescence as compared to that present in the acute phase of illness.

None of these patients was thought to have more than the moderate pharyngitis common to many acute respiratory infections and only 3 (Cases 19, 23 and 24) complained of sore throat. Two of these (Cases 19 and 24) were among the 3 patients (Cases 19, 21 and 24) who showed a significant rise in antistreptolysin titer. Of the other 3 patients, 2 (Cases 17 and 23) showed normal antistreptolysin levels without a significant rise in convalescence, the other (Case 1) showed a persistently high level, suggesting a carrier state following infection, of which, however, there was no history.

The benign rôle of beta-hemolytic streptococci in the patients with influenza is of interest since the combination might be expected to produce serious disease. That this may occur is evidenced by 1 patient, not included in this study, with a history and serologic evidence of a very recent influenza B virus infection who was admitted with a scarlatiniform rash and pneumonia, complicated by a massive pleural effusion, from whom beta-hemolytic streptococcus, Group A, Type 3, was recovered. Even with sulfadiazine and penicillin therapy, to both of which drugs

this organism was susceptible, this patient was critically ill for 7 days.

3. *Influenza Viruses.* No attempt was made to recover influenza virus from all patients. It is of interest that in 1945 the initial diagnosis of influenza in Case 17 was confirmed within 48 hours, by the recovery of influenza B virus from the throat washing. In every case, acute and convalescent sera were tested for antibodies against both influenza A and B viruses.

Influenza viruses possess the property of agglutinating erythrocytes of certain species. Without respect to recent infection many human sera possess the capacity, in greater or lesser degree, of inhibiting the phenomenon of hemagglutination. However, the agglutination-inhibition titer of serum from a patient convalescing from an influenza virus infection, when compared with the titer of serum obtained during the acute phase, usually shows a considerable increase directed specifically against the influenza virus (A or B) by which the individual was infected. If the agglutination-inhibition titer of a convalescent serum with respect to one or the other of the influenza viruses is 4 or more times greater than the acute phase serum titer, a diagnosis of infection by that influenza virus may be made with assurance.

In Table 1 the serum titers against both influenza A and influenza B viruses are expressed for each patient by a value representing the arithmetical increase of the convalescent titer as compared with the acute phase titer. For 2 patients (Cases 21 and 23) the actual titers are given since, although a rise could not be shown, they were each admitted after more than 1 week from onset with titers high enough to warrant a presumptive diagnosis of influenza.

It may be seen that during periods when infection by influenza viruses was prevalent many, but not all, of the cases of acute respiratory disease showed evidence of influenza virus infection. Of the 26 patients with respiratory disease admitted

Patient		Admission clinical impression	Duration of illness on admission (Days)	Laboratory findings					Serological findings					Final diagnosis	Case number
Case number	Age			Admission WBC (Thousands)	Pneumococcus (type)	Beta-hemolytic streptococcus (Group + type)	Non-hemolytic streptococcus (MG)	Pneumococcus agglutinins	Antistreptolysin O	Influenza virus agglutination inhibition		Streptococcus MG agglutinins	Cold hemagglutinins		
										A	B				
1943 - 1944															
1	18	PAP	8	95	0	A(?)	+	-	$\frac{200}{200}$	8	2	10	20	PAP Influenza A	1
2	36	PAP	3	75	0.	0	0	-	-	>8	1	10	0	Influenza A	2
3	24	Bronchitis	3	39	13	0	0	0	-	4	1	0	$\frac{40}{40}$	Influenza A	3
4	22	URI	6	75	0	0	0	-	-	16	12	0	0	Influenza A possible PAP	4
5	35	PAP	3	35	0	0	0	-	-	8	1	40	0	PAP Influenza A	5
6	35	PAP	4	61	0	0	0	-	-	1	1	20	20	PAP	6
7	21	PAP	4	68	34	0	0	0	-	1	1	20	40	Bronchitis resembling PAP	7
8	22	URI	4	77	0	0	0	-	-	8	1	0	0	Influenza A	8
9	25	Influenza	1	60	3	0	+	0	-	4	1	0	0	Influenza A	9
10	31	Influenza	5	52	0	0	0	-	-	32	1	0	0	Influenza A	10
11	38	Influenza	1	51	0	0	0	-	-	8	1	0	10	Influenza A	11
12	22	URI	2	92	6	G	0	0	-	4	1	10	0	Influenza A	12
1945 - 1946															
13	19	Influenza	1	73	0	0	0	-	-	13	64	0	0	Influenza B	13
14	22	PAP	5	69	7 direct	0	0	10	-	1	1	0	0	Pneumococcal pneumonia type 7	14
15	43	PAP	17	147	0	0	+	-	-	1	1	0	$\frac{80}{20}$	PAP	15
16	21	PAP	82	90	4 direct	0	+	0	-	1	29	10	0	Pneumococcal pneumonia type 4 Influenza B	16
17	18	Influenza	1	79	0	A, 17	+	-	$\frac{100}{75}$	08	8	0	0	Influenza B possible PAP	17
18	20	Influenza	1	149	19 direct	0	+	0	-	1	1	0	0	URI	18
19	18	Influenza	1	73	0	A(?)	+	-	$\frac{75}{250}$	1	15	$\frac{10}{10}$	0	Influenza B BHS infection	19
20	30	PAP	6	59	0	B	0	-	-	1	13	160	$\frac{160}{320}$	PAP	20
21	24	PAP	14	78	0	A, 3	0	-	$\frac{75}{150}$	$\frac{160}{80}$	$\frac{2560}{1280}$	$\frac{20}{20}$	0	PAP Influenza B BHS infection	21
22	18	PAP	8	80	43	0	+	0	-	1	1	0	0	Possible PAP	22
23	19	PAP	8	98	28 direct	A(?)	0	0	$\frac{75}{100}$	1	$\frac{2560}{1920}$	40	$\frac{20}{80}$	PAP Influenza B	23
24	17	Influenza	1	77	15	A, 3	0	0	$\frac{500}{500}$	3	08	20	40	Influenza A BHS infection	24
25	18	PAP	5	176	7	0	0	10	-	1	1	0	0	Pneumococcal pneumonia type 7	25
26	18	PAP	3	38	8	0	0	10	-	15	1	0	0	Pneumococcal pneumonia type 8	26

TABLE 1.—P.A.P. = Primary Atypical Pneumonia. U.R.I. = Upper Respiratory Tract Infection. B.H.S. = Beta-hemolytic Streptococcus. * = Single figures in these columns represent the highest serum titer observed in convalescence, where the acute phase serum titer was <5 (pneumococcus agglutinins) or <10 (streptococcus MG agglutinins and cold hemagglutinins). † = Where figures appear as fractions the numerator represents the serum titer on admission, the denominator represents the serum titer in convalescence. ** = Influenza virus agglutination inhibition titers are represented by a figure denoting the arithmetic increase of convalescent serum titer over acute-phase serum titer. § = This patient developed significant mouse-protective antibody against his pneumococcus.

during 2 epidemic periods, 17 showed evidence of infection with an influenza virus. One patient (Case 24) gave evidence of influenza A virus infection at a time when influenza B was epidemic. The antibody titer of this patient's convalescent serum was only 3 times greater than that of his acute phase serum. However, this increase was repeatedly demonstrable, was apparent also in a chick embryo protection test, and is very probably significant. Attempts to recover influenza virus from this patient were unsuccessful. This patient illustrates the fact that cases of infection by one of the influenza viruses when the other virus is epidemic, though uncommon, do occur.

Cases 4 and 17 showed serologic evidence of influenza virus infection, and influenza B virus was recovered from Case 17. Case 4 presented physical and Roentgen ray signs of pulmonary involvement on admission. In Case 17 a hazy but definite right lower lobe shadow, not present on admission, was seen in a Roentgen ray on the 4th day; it disappeared during convalescence, and was unaccompanied by physical signs. In Case 4, no significant bacteria were recovered. Case 17 showed in throat culture beta-hemolytic streptococcus, Group A, Type 17, but antistreptolysin O tests gave no evidence that this organism had caused infection. Both cases, therefore, represent examples of influenza virus infection associated with pneumonia of undetermined etiology, and again raise the question of whether the influenza viruses, which are capable of causing pneumonia in other susceptible species, are also capable of effecting a similar pathologic pattern in man.

4. *H. Influenzæ Group*. Organisms resembling *H. influenza* were recovered from 6 patients (Cases 5, 6, 16, 17, 22 and 23); none was typable and except in 1 patient (Case 22) in which they were the predominant organism in the sputum, they were present only in small numbers.

5. *Non-hemolytic Streptococcus (MG)*. Eight patients (Cases 1, 9, 15, 16, 17, 18, 19 and 22) showed streptococcus MG in

cultures of sputum or throat. Of these, only 2 (Cases 1 and 16) developed agglutinins against this organism. The incidence of streptococcus MG in this study is similar to that previously found in various types of respiratory disease.⁵ The mere isolation of this organism from the sputum or throat appears not to be of diagnostic import.

6. *Cold Hemagglutinins and Streptococcus MG Agglutinins*. The development in the serum of a patient with pneumonia of cold hemagglutinins⁴ or of agglutinins against a non-hemolytic streptococcus designated as streptococcus MG,⁵ is of confirmatory value in making a diagnosis of primary atypical pneumonia.

The available published data on both these tests have been summarized in a recent discussion by Horsfall.³ Streptococcus MG agglutination tests have been reported on more than 1000 persons who can be divided into 3 groups: those with a clinical diagnosis of primary atypical pneumonia, those with clinical diagnoses of other acute infections, and normal persons. Streptococcus MG agglutinin titers of 1:20 or more were found in the sera of approximately half (48.9%) of the patients with primary atypical pneumonia, whereas in each of the other 2 groups comparable titers were found in only 5%. When acute phase and convalescent serum titers were compared, significant increases in titer (fourfold or more) were limited with but rare exception to primary atypical pneumonia. The published data on the occurrence of cold hemagglutinins in similar groups provide information on more than 2000 persons upon whose sera the test was carried out in a standard manner. Titers of cold hemagglutinins of 1:40 or more were found in the sera of 54.4% of the primary atypical pneumonia group, in 2% of the group with "other infections" and in none of the "normals."

The significance of the occurrence of either of these agglutinins in normal persons or in patients with acute infections other than primary atypical pneumonia, cannot as yet be determined. Where the

clinical diagnosis of an acute respiratory disease associated with pneumonia is doubtful, a convalescent rise in the titer of either agglutinin to a level of 1:20 or more suggests that the disease should be classified as primary atypical pneumonia. It is of interest that such a rise in either or both agglutinins developed in 9 patients in the present series, of whom 8 had physical or Roentgen ray signs of lung involvement, and in only 1 of 6 patients without positive lung findings. The results of streptococcus MG agglutination and cold hemagglutination tests are recorded in Table 1.

Patients with Titers of Streptococcus MG Agglutinins or Cold Hemagglutinins of 1:20 or More. Titers of either agglutinin attained levels of 1:20 or more in the convalescent sera of 8 patients (Cases 1, 5, 6, 7, 15, 20, 23 and 24). In 2 patients agglutinin titers were in this range on admission and remained constant until discharge; Case 21, admitted on the 14th day following onset showed an agglutination titer against streptococcus MG of 1:20, and Case 3 maintained a constant cold hemagglutination titer of 1:40.

Of this group, 3 patients (6, 15 and 20) appeared clinically and on the basis of these serologic tests, to have primary atypical pneumonia; in none of them were the bacteriologic or other serologic findings of positive diagnostic significance.

The presence of significant titers of either of these agglutinins is somewhat more difficult to interpret in Cases 1, 5 and 23. In each of these cases the illness and Roentgen ray findings were consistent with atypical pneumonia. In addition, however, all presented serologic evidence of infection by one of the influenza viruses, and from Cases 1 and 23 a Group A beta-hemolytic streptococcus was recovered. In the last 2 patients there was no serologic evidence that hemolytic streptococcus was implicated in the disease. In Case 1 the cold hemagglutinin titer of 1:20 favors a diagnosis of primary atypical pneumonia; a titer of this height is rare in influenza, but occurs frequently in primary

atypical pneumonia. The simultaneous rise in streptococcus MG agglutinins supports this interpretation, since the titers of this agglutinin have not been observed to increase as a result of influenza. In Cases 5 and 23 diagnosis is less difficult, since both developed streptococcus MG agglutinin titers of 1:40, and Case 23 also acquired a cold hemagglutinin titer of 1:80. The possibility that Type 28 pneumococcus played a part in the latter patient's disease has already been considered to be unlikely. In these 3 patients the evidence suggests concurrent infection by one of the influenza viruses and the agent or agents responsible for primary atypical pneumonia. It is probable that Case 21 also belongs in this group. This patient was admitted late in the course of illness and maintained a constant titer of agglutinins against streptococcus MG of 1:20. He also showed evidence of influenza B virus infection, and carried Group A hemolytic streptococcus, with serologic evidence of infection by this organism.

Case 7 had an illness clinically resembling primary atypical pneumonia with physical signs of lung involvement but without Roentgen ray evidence of pneumonia. During convalescence this patient developed a titer of 1:20 against streptococcus MG and a cold hemagglutinin titer of 1:40. Case 24 developed both streptococcus MG agglutinins (1:20) and cold hemagglutinins (1:40) without physical or Roentgen ray evidence of pneumonia; the relationship of these agglutinins to the patient's disease, in which there was serologic evidence of infection by both influenza A virus and Group A hemolytic streptococcus, is not apparent. Case 3 had an influenza A virus infection, with acute bronchitis without Roentgen ray evidence of pneumonia. Serum obtained on the 3rd day of illness possessed a cold hemagglutinin titer of 1:40, which persisted during his hospital stay. To which aspect of his illness this should be ascribed is impossible to decide.

Patients With Titers of Streptococcus MG Agglutinins or Cold Hemagglutinins of Less

than 1:20. The sera of 5 patients (Cases 2, 11, 12, 16, 19) showed either streptococcus MG agglutinins, or cold hemagglutinins in a titer of less than 1:20, but in the first 4 instances this represented an increase in titer. It may be of significance that in each of these 4 cases there was physical evidence of lung involvement, although in Case 16, the only one with Roentgen ray evidence of pneumonia, Type 4 pneumococcus appeared to be the etiologic agent. In addition each of these 4 cases gave serologic evidence of influenza. The remaining patient (Case 19) had neither physical nor Roentgen ray signs of pneumonia, but showed serologic evidence of both influenza and Group A beta-hemolytic streptococcus infection, with a streptococcus MG agglutinin titer of 1:10 which remained unchanged during his hospital stay.

In these cases no reliable interpretation of either streptococcus MG agglutinin or cold hemagglutinin titers of less than 1:20 appears to be possible.

7. Patients Without Positive Serologic Response. Cases 18 and 22 failed to develop demonstrable antibodies against the pneumococci isolated from them, or either of the influenza viruses, and did not develop either cold or streptococcus MG agglutinins.

CLINICAL IMPRESSIONS ON ADMISSION AND THEIR RELATION TO FINAL DIAGNOSIS. From the serologic data it appears that in these patients with acute infections of the respiratory tract, a number of different infectious agents (including the agent or agents of primary atypical pneumonia) were responsible for the illnesses observed, and furthermore, that in certain instances 2 or more infectious agents were implicated together. The question which is of present interest is whether the laboratory findings, the clinical impression in each case, and the final classification of the patient's disease may be integrated. An attempt to establish such correlations discloses some of the difficulties and errors often encountered but more often overlooked in the diagnosis of these diseases.

It was the practice in each case to record a clinical impression before the results of Roentgen ray or laboratory examinations were known. In Table 2 the presenting symptoms and relevant physical findings of each of the patients under consideration are shown, with the clinical impression and final diagnosis.

1. *Beta-hemolytic Streptococcal Infections.* In none of the initial clinical impressions was the possibility considered that these patients might have beta-hemolytic streptococcus infections, yet from 6 cases a Group A organism was isolated, and in 3 serologic evidence of infection was also obtained. In none of these patients did the signs or symptoms suggest infection by this organism.

2. *Influenza.* A diagnosis of influenza was made on admission in 8 patients (Cases 9, 10, 11, 13, 17, 18, 19 and 24) and in 7 it remained the final diagnosis. Case 18, the exception, is discussed below. It is significant, in view of the number of patients shown to have an influenza virus infection which was not diagnosed clinically, that all of these patients were admitted to the hospital on the 1st day of their illness, with the exception of Case 10, a physician who treated himself at home. All of these patients were acutely ill and were hospitalized promptly. The fact that the initial diagnoses in these cases were correct may be attributed in part to accurate appraisal of the clinical manifestations of acute infection with relatively marked constitutional symptoms, observed soon after the abrupt onset, but chiefly to the fact that the patients presented symptoms that were compatible with a diagnosis of influenza at a time when influenza (A or B) was known to be present in epidemic form.

In the 7 patients with influenza whose disease was diagnosed correctly on admission, the symptoms were varied. In all the onset of the illness was sudden, and in only 2 was it preceded by respiratory symptoms of any sort. All of the patients had fever. All but 1 of the patients had a cough, but in only 4 (Cases 11, 17, 19

Patient		Admission clinical impression	Duration of illness on admission (Days)	Symptoms (in order of frequency)											Abnormal lung findings (location)		Final diagnosis	Case number
Case number	Age			Malaise and fever	Cough	Sudden onset	Headache	Generalized aching	Sputum	Rigor	Previous U.R.I	Sore throat	Epistaxis	Nausea	Vomiting	Physical		
1943 - 1944																		
1	18	P.A.P.	8												LL	LL	P.A.P. Influenza A	1
2	36	P.A.P.	3												RL LL	0	Influenza A	2
3	24	Bronchitis	3												LL	0	Influenza A	3
4	22	U.R.I	6												RL	RL	Influenza A possible P.A.P	4
5	35	P.A.P.	3												RL	RL	P.A.P Influenza A	5
6	35	P.A.P.	4												LL	LL	P.A.P.	6
7	21	P.A.P.	4												LL	0	Bronchitis resembling P.A.P	7
8	22	U.R.I.	4												0	0	Influenza A	8
9	25	Influenza	1												0	0	Influenza A	9
10	31	Influenza	5												0	0	Influenza A	10
11	33	Influenza	1												RL LL	0	Influenza A	11
12	22	U.R.I	2												RL	0	Influenza A	12
1945 - 1946																		
13	19	Influenza	1												0	0	Influenza B	13
14	22	P.A.P	5												0	RL	Pneumococcal pneumonia type 7	14
15	43	P.A.P.	17												RL	RL	P.A.P.	15
16	21	P.A.P.	8?												RU	RU	Pneumococcal pneumonia type 4 Influenza B	16
17	18	Influenza	1												0	RL	Influenza B possible P.A.P	17
18	20	Influenza	1												0	0	U.R.I.	18
19	18	Influenza	1												0	0	Influenza B B.H.S infection	19
20	30	P.A.P	6												RL	RL	P.A.P.	20
21	24	P.A.P.	14												RL	RL	P.A.P Influenza B B.H.S infection	21
22	18	P.A.P.	8												0	RL	Possible P.A.P	22
23	19	P.A.P	8												RL	LL	P.A.P Influenza B	23
24	17	Influenza	1												0	0	Influenza A B.H.S infection	24
25	18	P.A.P.	5												RL	RL	Pneumococcal pneumonia type 7	25
26	18	P.A.P.	3												0	LL	Pneumococcal pneumonia type 8	26

TABLE 2.—P.A.P. = Primary Atypical Pneumonia. U.R.I. = Upper Respiratory Tract Infection. B.H.S. = Beta-hemolytic Streptococcus. RL, LL = Right lower lobe, left lower lobe, etc.; refers to area of lung in which any abnormal findings from persistent râles to signs of consolidation were localized.

and 24) was it productive. In 4 of the patients the onset of disease was accompanied by a rigor, and in 1, such chills recurred for some days. Six of the patients complained of generalized aching, the other did not. Among other symptoms may be mentioned headache in 5, sore throat in 4, nausea and vomiting in 1, and epistaxis in another. Positive physical findings were few. All of the patients looked acutely ill, and all had a mild to moderate degree of nasopharyngitis. Only one showed flushing of the face and upper thorax, so often described as "typical." One patient had a few râles at 1 lung base (Case 11) and another (Case 17) developed a right lower lobe shadow late in his disease. All the leukocyte counts were normal. In 3 patients the sedimentation rate was normal (less than 10 mm.) on admission, and remained so; the other 4 patients (Cases 10, 11, 19 and 24) had elevated rates around 30 mm. which persisted to the time of discharge.

Case 24, in whom positive clinical findings were limited to a moderate nasopharyngitis, presented a puzzling array of laboratory findings, with initial neutropenia and the recovery of Group A beta-hemolytic streptococcus, Type 3, from his throat, and pneumococcus, Type 15, from sputum after mouse inoculation. In this case the convalescent titers of influenza A virus antibody and antistreptolysin are interpretable; the development of significant titers of both streptococcus M₁₆ agglutinins and cold hemagglutinins, is not.

Case 18, diagnosed as influenza, had an acute upper respiratory tract infection, with fever lasting only 24 hours. Type 19 pneumococcus was found on direct typing of his sputum, and his white blood cell count was elevated. Serologic tests failed to confirm the clinical diagnosis, and did not provide any positive evidence that the pneumococcus was implicated in his disease.

3. "*Upper Respiratory Tract Infection.*" Three cases called upper respiratory tract infection on admission (Cases 4, 8 and 12) were later shown to have had influenza A

virus infections. These individuals presented no very different symptoms from the previous group, but this non-committal diagnostic impression may have been determined by the fact that they were first seen on the 6th, 4th and 2nd days, respectively, of their illnesses, when the symptoms and findings at onset were a matter of history rather than observation.

The admission white blood counts in these cases ranged from 7.2 to 9.2 thousand. On admission no significant organisms were identified with the exception of Type 6 pneumococcus in Case 12, which was recovered only on mouse inoculation of sputum.

The admission impressions were modified in Cases 8 and 12 only by the serologic evidence of influenza A infection. In Case 4 the demonstration of a shadow in the right lower lobe on admission Roentgen ray before physical signs were evident, changed the clinical impression to primary atypical pneumonia. Later serologic tests showed that the patient had had influenza A infection, but gave no confirmatory evidence regarding the cause of his pneumonia, which remains undetermined, although it may belong in the primary atypical pneumonia group.

4. *Acute Bronchitis.* In a single patient (Case 3) an admission diagnosis of bronchitis was made. Although this patient had signs of bronchitis his illness was not distinguishable from many others in the group, and from the laboratory evidence only a diagnosis of influenza A could be made. The occurrence of a constant moderately high level of cold hemagglutinins in his serum is unexplained.

5. *Primary Atypical Pneumonia.* The clinical impression of primary atypical pneumonia was recorded on admission for 14 patients. In contrast to the group initially diagnosed as influenza, only 2 of this group of patients were seen as early as the 3rd day of illness, and the average duration of illness before admission was 6.8 days. Serologic evidence confirmed the admission impression in 8 cases; in the 6 remaining cases, a different diagnosis

was established in 5, and in 1 a positive diagnosis was not established. In several instances serologic results necessitated additional diagnoses, principally of influenza A or B.

Cases in Which the Clinical Impression of Primary Atypical Pneumonia Was Confirmed Serologically. In 7 patients (Cases 1, 5, 6, 15, 20, 21 and 23) both Roentgen ray and serologic findings confirmed the admission impression of primary atypical pneumonia, and in an additional patient (Case 7) the clinical and serologic findings warrant the inclusion of the patient in this group, although Roentgen ray evidence of pneumonia was lacking. In this group of patients symptoms were variable and there was no significant clinical difference between those who had concurrent influenza and those who did not. Except for the results of chest examinations the physical findings were not very striking. These patients were neither so acutely ill nor so prostrated as patients with uncomplicated influenza and Case 5 was the only patient whose course suggested that concurrent influenza and primary atypical pneumonia may be more severe than either disease alone. The average white blood count on admission was 9.6 thousand. There was 1 example of leukopenia (Case 5, with concurrent influenza) and 1 of leukocytosis (Case 15). The sedimentation rate was elevated in all patients except Case 4. Admission bacteriologic findings did not lead to any alterations of the original clinical impressions, although Group A beta-hemolytic streptococci were recovered from 3 of the patients (Cases 1, 21 and 23). There was no clinical evidence suggesting infection by these organisms. From Case 23 Type 28 pneumococcus was identified directly in sputum, but its significance was doubtful.

Serologic results confirmed the diagnosis of primary atypical pneumonia in all of these patients, and led to additional diagnoses of influenza virus infection in Cases 1, 5, 21 and 23. Cases 1 and 5 gave evidence of concurrent influenza A; both Cases 21 and 23 showed presumptive evi-

dence of influenza B, with very high antibody levels on admission (the 14th and 9th days, respectively of their illnesses). The history of Case 21 suggested 2 distinguishable but merging episodes of infection of which the first probably represented influenza B, and the second, primary atypical pneumonia; in the other patients no such biphasic pattern could be made out. In Case 21, serologic findings necessitated a third diagnosis of concurrent beta-hemolytic streptococcus infection; in Cases 1 and 23, from whom this organism was also recovered, serologic evidence did not suggest that streptococcal infection played a part in their disease.

Cases in Which the Clinical Impression of Primary Atypical Pneumonia Was Erroneous or Not Established. Cases 2, 14, 16, 22, 25 and 26 were thought to have primary atypical pneumonia on admission. Of these, Cases 14, 16, 25 and 26 are of particular interest since all appear to have had pneumococcal pneumonia. These 4 patients were first seen relatively late in their illnesses and only 1 presented physical signs of pulmonary involvement. In 2, previous therapy had very probably altered the course of the disease, so that the patients did not seem particularly ill. Admission white blood counts of the 2 untreated patients (Cases 14 and 16) were 6.9 and 9 thousand, respectively. Case 25, who had received penicillin, had a white blood count of 17.6 thousand and Case 26, previously treated with sulfadiazine, a leukocyte count of 3.8 thousand. The appearance of these 4 patients' lungs in Roentgen ray films seemed of significance in retrospect, since all had hazy, rather evenly diffuse pulmonary shadows, which with 1 exception were located peripherally. This appearance is not in itself diagnostic, but differs from the common picture in primary atypical pneumonia. In each of these cases the provisional diagnosis was almost immediately made doubtful by the finding of significant types of pneumococci in the sputum. Direct identification of Type 7 (Case 14) and Type 4 pneumococcus (Case 16) was possible; in

the 2 previously treated patients pneumococci were recovered after mouse inoculation, Type 7 from Case 25 and Type 8 from Case 26.

In order to establish the rôle of pneumococci recovered from these patients with illnesses which deviated from the usual picture of lobar pneumonia, it was necessary to show that the patients had developed antibodies directed against the type of pneumococcus recovered. Cases 4, 15 and 26 developed agglutinins against their own organisms and did not develop agglutinins against a heterologous type (Type 1). Case 16 failed to develop agglutinins but did develop a significant level of mouse-protective antibodies against his own organism. In addition there was serologic evidence of concurrent influenza B in this patient.

Two remaining patients were thought on admission to be examples of primary atypical pneumonia (Cases 2 and 22). Case 2 had a severe paroxysmal cough, with inconstant râles at both lung bases on admission. There was no Roentgen ray evidence of pneumonia. He developed antibodies against influenza A virus, and was finally classified as influenza A with bronchitis of undetermined etiology. Case 22 had the clinical appearance of atypical pneumonia, with pneumococcus Type 43 recoverable from his nose, throat and sputum. His serum gave only negative results in all tests performed. The final diagnosis was pneumonia of undetermined etiology, but it is possible that this patient is actually an example of primary atypical pneumonia.

RÉSUMÉ OF FINAL DIAGNOSES. *Cases for Which a Single Infectious Agent Appeared Responsible.* In 10 patients (Cases 2, 3, 4, 8, 9, 10, 11, 12, 13 and 17), the bacteriologic and serologic findings suggest that one or the other of the influenza viruses was the sole etiologic agent involved. However, 5 of these patients (Cases 2, 3, 4, 11 and 12) showed localized râles, and 1 of these (Case 4), as well as in Case 17, there was Roentgen ray evidence of pulmonary infiltration. No additional evi-

dence could be adduced to explain these lung findings.

Four patients (Cases 6, 15, 20 and 7) appear to belong in the primary atypical pneumonia group. Clinical and laboratory evidence in the first 3 causes them to be so classified, and the evidence suggests that Case 7, despite the absence of pneumonia in Roentgen ray films, belongs in this category.

In 3 patients (Cases 14, 25 and 26) pneumococcus appeared to be the sole etiologic agent. In 2 patients (Cases 18 and 22) the etiology remains doubtful.

Cases for Which More Than One Infectious Agent Appeared Responsible. In the remaining 7 patients the effects of more than 1 infectious agent must be considered. In 2 instances (Cases 19 and 24), although influenza virus infection appeared to be responsible for the clinical manifestations, there is evidence that concurrent infection by beta-hemolytic streptococcus occurred. In 1 instance (Case 16) concurrent infection by influenza B virus and pneumococcus Type 4 appears to have taken place. There is a further group of 4 patients (Cases 1, 5, 21 and 23) in which infection by an influenza virus and the agent or agents of primary atypical pneumonia appear to have occurred at approximately the same time, and in 1 of these (Case 21) infection by beta-hemolytic streptococcus also occurred.

DIAGNOSTIC ERRORS. On comparing the clinical impressions with the final diagnoses, as has been done graphically in Figure 1, two principal errors stand out. The first, an error of omission, was failure to suspect the rôle of the influenza viruses in many of these cases. This became evident, in most instances, only after serologic tests had been done, and was particularly striking in those patients with pneumonia which presumably was due to another agent. Multiple diagnoses are commonly viewed with suspicion, for it is well known that a single pathologic process may manifest itself in various organs in such a manner as to suggest that more than 1 disease is present. The present

studies indicate that what appears to be a single disease picture with involvement of a system, the respiratory tract, may be associated with infection by more than 1 infectious agent, and in most instances it is impossible to judge whether one or another of the agents plays a "primary" or "secondary" rôle.

The second principal error, one of commission, was the classification as primary atypical pneumonia of cases with other infections. This occurred most often with pneumococcal pneumonias which showed an atypical onset or course. It seems obvious that the similarities among acute respiratory tract infections of different

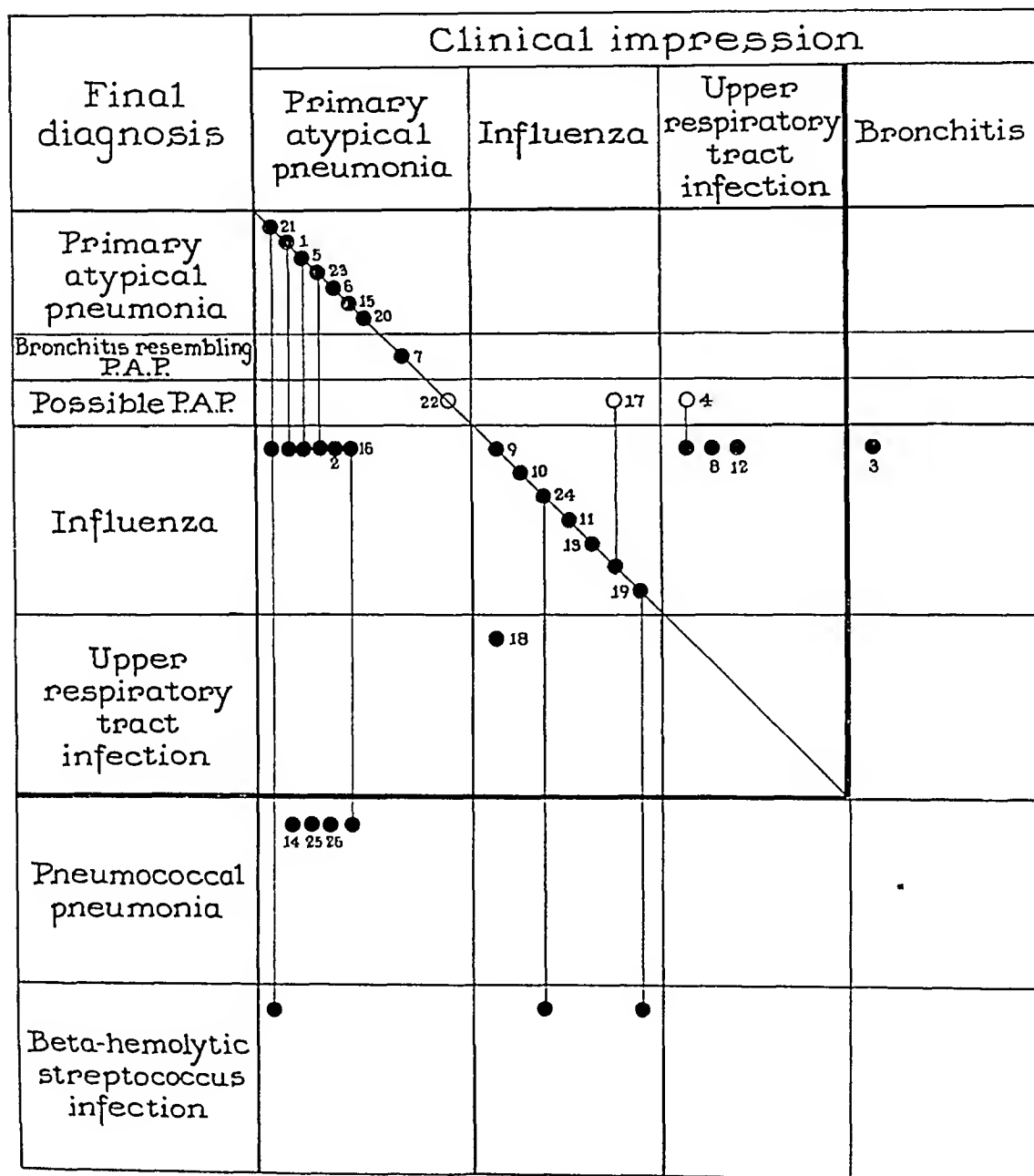


FIG. 1.—Graphic comparison of original clinical impressions with final diagnoses. Each numbered circle denotes a single patient. Each solid circle represents a single diagnosis, and solid circles connected by a vertical line represent multiple diagnoses in a single case. Clinical impressions confirmed by laboratory tests are represented by circles lying on the oblique line; circles distant from the line represent clinical errors of varying degree. Open circles represent cases in which positive serologic evidence for satisfactory classification was lacking.

etiologies are considerably more striking than the differences; although a correct diagnosis may be reached by clinical methods, such a diagnosis cannot be considered as established without a considerable amount of laboratory evidence.

Fashions in terms play their part in erroneous diagnosis and "primary atypical pneumonia" is a case in point. On clinical grounds alone a wide variety of different infections might be classified as primary atypical pneumonia. At the present time an accurate diagnosis in this disease rests largely upon the weight of negative evidence; *i. e.*, the exclusion of a number of specific infectious diseases, any one of which may closely simulate this condition. At the present time most workers agree that only 2 laboratory procedures, *e. g.*, cold hemagglutination and streptococcus MG agglutination, give positive assistance in the diagnosis of this disease, and yet it appears that either test is positive in not more than 50% of cases.

In the present state of knowledge of acute respiratory infections certain broad diagnostic terms might be applied to those conditions in which it is not possible or not feasible to establish a diagnosis with laboratory evidence. While the use of such terms as "catarrhal fever" or "upper respiratory infection" is indefensible if facilities are available for establishing a more accurate diagnosis, it is preferable to the use of "primary atypical pneumonia" or "influenza" when these diagnoses are not or cannot be substantiated. In the absence of adequate laboratory evidence the terms "acute respiratory tract infection" and "acute respiratory tract infection, with pulmonary involvement" are about as specific as the facts will allow in the great majority of acute respiratory ailments.

IMPORTANCE OF CORRECT DIAGNOSIS.
From the point of view of the patient

accurate diagnosis is chiefly important as a basis for appropriate therapy. In acute respiratory infections there appears to be a tendency now to reverse the usual procedure and diagnosis is often dependent upon the effects of therapy. This is open to serious criticism, for aside from the hazards of adequate sulfonamide therapy and the difficulties and expense of adequate "antibiotic" therapy, there is the impossibility, when they are used blindly, of interpreting results, and the further real danger that diagnosis may be left to the academician. It has been suggested that therapeutic agents may in the future be developed, the range of efficacy of which may be so wide as to relegate diagnosis in certain infectious diseases to the class of a minor art. There is equally good reason to believe, however, that the further development of therapeutic agents may make available substances with a high degree of specificity, both in their therapeutic range and in their point of attack upon the infectious agent, and that their proper use may depend upon a diagnostic accuracy which has not yet been achieved with respect to acute respiratory tract disease.

Summary. The difficulties of accurate diagnosis in acute respiratory infections are brought out by relating in a group of such cases the clinical impression on admission with laboratory findings early and in convalescence, and with the final diagnoses arrived at after the accumulation of all the pertinent data. It is shown that concurrent infection by more than one infectious agent may occur often. It is suggested that in the absence of confirmatory laboratory evidence supporting a specific diagnosis, non-specific terms be used to describe acute respiratory infections. It is also suggested that modern therapeutic agents may require more, rather than less, diagnostic accuracy for their effective use.

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THE CHANGING CONCEPT OF MYELOMA OF BONE

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MYELOMA is no longer considered an unusual disease. Over 1000 cases are reported in the literature on the subject. To add a series of 13 cases studied at Temple University Hospital merely to review the usual clinical, laboratory and morbid anatomical findings would add little of value to what is already known. But, whereas the disease today is probably no different than it was in 1850 when McIntyre first described it, in the last ten years there has been a very definite change in our concept. In 1928 Ewing⁶ wrote, "Multiple myeloma is a specific malignant tumor of the bone marrow, arising probably from a single cell-type, and characterized chiefly by multiple foci of origin, a uniform and specific structure composed of plasma cells or their derivatives, rare metastases, albumosuria, and a fatal termination." Today we must admit that the tumor may possibly arise from extra-medullary sources, that it is probably not of a single cell origin, that it may have a single focus for a considerable period or it may be so diffuse that no foci are apparent and that it may be composed of other than plasma cells.

The change in our concept of this tumor involves principally (1) a better understanding of the subtypes, (2) its complex cytogenesis, (3) some recently developed laboratory diagnostic procedures and (4) the nature and kind of bone demineralization which it induces. The purpose of this discussion is to emphasize these aspects. The salient data concerning our cases are included not as case reports of an unusual disease, but to serve as a basis for the discussion.

SUBTYPES. Today we must recognize at least three subvarieties of this disease.

The classical type occurs as multiple tumors arising in red marrow. They may occur simultaneously or successively over a period of months. Seven of our cases proved eventually to be of this type. The tumors occur preponderantly in flat bones and exclusively in areas where red marrow is found. In the age group most commonly affected (40 to 60 years) hematopoiesis is restricted to flat bones and the metaphyses. The tumor may rarely occur in younger patients.¹⁵ Two in our series were under 40, one aged 32 and the other 16. In these two alone were the long bones affected. The remarkable lytic action of the tumor cells on the contiguous bone makes this type the easiest to diagnose. Indeed, the diagnosis may be made in many cases on examination of Roentgen-ray films of the flat bones.

A second subtype may begin as a single focus and remain solitary for a variable length of time. Reports of such cases are not uncommon.^{4,11,14} Paul and Pohle¹⁴ gave an excellent account of five such tumors. There has been a tendency to classify these separately under the heading of "solitary myeloma." There seems to be scant evidence, however, that the myeloma may exist in the solitary form indefinitely and so deserve a separate classification. All completely studied cases of a single lesion which we have encountered have eventually shown multiple foci. Four of our series were discovered in the single tumor stage. In three a single lesion was found in one of the lumbar vertebrae, in a fourth the tumor was located in the neck of the femur. All of these tumors became multiple within nine months.

A third subtype of myeloma appeared to be so generalized that practically all red

marrow is affected simultaneously. It is this type which produces generalized skeletal demineralization and consequent profound changes in the peripheral blood. Two of our cases were of this nature. It was these cases which aroused our interest in this subject since both cases were misdiagnosed on the original Roentgen-ray studies as idiopathic senile osteoporosis. Both were in elderly patients and both showed marrow replacement by tumor plasma cells throughout the flat skeleton. Any of the above varieties may produce soft tissue metastases in the later stages of the disease, but these are usually found to be extra-medullary extensions rather than true metastases. However, unquestionable soft tissue tumors have been reported though these are exceptional.

Another type of tumor which probably is better designated as myelocytoma rather than myeloma is solely or predominantly confined to soft tissues. Hellwig⁹ gives an excellent review of 127 such cases and Esposito and Stout⁵ add one of their own. They were found predominantly in the upper respiratory passages and the conjunctiva with a few in the small intestine. There is considerable uncertainty among morphologists as to whether this type represents a separate tumor entity or whether it should be considered a subvariety of the marrow type. Its behavior is completely different since its growth is phlegmatic and it may be cured by complete removal. Though its component cells are impossible to distinguish morphologically from some of the marrow tumors its clinical features are so different that it seems best to exclude it from this discussion.

CYTOGENESIS. The cytogenesis of myeloma is still poorly understood. It is now certain that the plasma cell myeloma is but a single, though the most common, type. A number of excellent papers have appeared recently presenting evidence of the protean genesis of this group. Some writers believe that young forms of both the myelogenous and erythropoietic series may assume neoplastic propensities and

produce myelomas of a particular cell type. Herbut and Erf^{3,10} have recently described tumors which behaved like myelomas and which they believed to arise from megakaryocytic and lipoblastic marrow elements. One is reminded of the dangers in hypothesizing on tumor cell origins on the basis of static morphology alone. While such a concept seems startling, if we accept the hypothesis that all marrow elements are of mesenchymal origin along with the fibrous, cartilaginous and bone tissue, one is forced to admit that such tumors, at least the megakaryocytoid type if such a tumor exists, could be classified as a myeloma in its broadest sense. In such a classification the Ewing's tumor might also belong in the myeloid group. Its clinical features are not too dissimilar except in regard to the age group affected. Its cytology is certainly consistent with a marrow origin and its site of predilection is explained by the red marrow distribution at this age.

In short, the number of these various tumors of marrow cells included under the heading of "myeloma" depends upon the inclination of the writer. From the clinical standpoint the entire group may be considered together. They begin in the marrow of flat bones and long bones in young patients and almost exclusively in flat bones in the older group. They may be single at first but eventually become multiple. They show varying degrees of lytic action on bone and, in all, the eventual prognosis is hopeless.

From the cytomorphologic standpoint there are but two clearly defined types, the plasma cell myeloma and the Ewing's tumor. This leaves a considerable number which can be differentiated on the basis of cytologic character alone. It is agreed by all that these tumors arise from various of the marrow elements; it is unfortunate that the limitations of microscopic study prevent us from knowing exactly which one. One feature of interest is brought out by examination of aspirated sternal marrow. Such material from 57 of our cases was studied. One showed no mye-

loma cells. Of the other 4, two were of the myeloid and 2 of the plasma cell type as diagnosed on sectioned tissue taken directly from the tumors. Yet, in all 4 instances the marrow smears showed nearly identical tumor plasma cells. Seven of our series were of the classical plasma cell variety, while 6 were "myeloid" in type.

Lowenhaupt¹² and others consider the plasma cell type to arise from the reticulo-endothelial elements of marrow and elsewhere, particularly the spleen. This concept makes myeloma a diffuse process which in a sense is comparable to the leukemias. In the three cases of our series which were autopsied there were abnormal numbers of plasmocytes in the splenic sinuses and some of these were multinucleated. Two of these spleens were smaller than normal, while only one was enlarged (300 gm.).

LABORATORY PROCEDURES. Many cases of myeloma develop signs and symptoms of kidney insufficiency. There has been great controversy concerning this complication. Some writers contend that the passage of Bence-Jones protein caused glomerular damage with resultant functional impairment, but Bell,¹ and Forbus⁷ et al. have described the kidneys of myeloma cases and attempted to produce kidney damage experimentally by forced excretion of this material. Both are definite in their statements that the protein acts only as foreign body casts which block the tubules. Ehrlich described this tubular obstruction by Bence-Jones protein casts and applied the term "internal hydronephrosis." This explanation of renal insufficiency seems logical except that no mention of anuria or oliguria is made, and if the damage is dependent on mechanical fluid obstruction, it would seem that curtailed urine excretion would of necessity be a symptom. Of our 3 autopsied cases, cast formation was marked in one, slight in another and entirely lacking in the third. Bence-Jones protein was found in the urine of none of these patients, though admittedly it may have been tran-

sient and lacking only at the time at which the test was made. Of these 3 cases only the one with casts suffered from impaired renal function. But at no time was there a subnormal urine output, though there was a consistent cloud of albumin. One is led to wonder if the casts in the tubules in this patient were artefacts, the result of the coagulating action of the fixative upon the increased protein in the fluid urine. The glomeruli showed a fibrinoid type of degenerative change which may have accounted for the functional disturbance.

It is generally believed that the Bence-Jones protein is derived from the myeloma cells and/or the cells of normal bone marrow. Its excretion through the glomeruli is partially explained on the basis of its molecular weight which is about half that of serum albumin, although another factor is apparently involved. It is predominantly a beta globulin.² The reticulum and at least some of its derivatives are active in the formation of globulin, and in antibody production. The association of increased plasma globulin and the presence of abnormal numbers of plasmocytes is encountered in numerous diseases. It would seem possible that the type and the increase in amount of the globulin present in some cases of myeloma may depend upon the type of marrow cell from which the tumor derives. Whatever the cause of the renal insufficiency, chemical examination of the blood and urine should be made in all cases suspected of myeloma. If protein is present in the urine it should be examined for Bence-Jones bodies.

Bence-Jones protein is probably not as commonly present as the earlier accounts would lead one to believe, or it may be transient and missed on one or even more analyses. Most recent accounts give an incidence considerably below the 73% originally reported. It was looked for in 12 of our cases but found in only 1. However, large amounts of albumin were found in 3 others. Hyperproteinemia was found in 3, hyperglobulinemia in 2 (examined for in only 5) and hypercalcemia in 3. In 10 cases a definite anemia was present and in

FIG. 1

Case No.	Age	Subtype	Cell Type	Area	Serum Calcium (mg. per 100cc.)	Serum Phosphorus (mg. per 100cc.)	Total Protein (Gm. per 100cc.)	Albumin (Gm. per 100cc.)	Globulin (Gm. per 100cc.)	R.B.C. (Million)	Sedimentation Rate (mm. per hr.)	Leucocytes	Urine Albumin	Bence-Jones Protein
1	M	60	Diffuse	Plasma Cell	All Red Marrow	13	5.2	7.3	5	2.3	3.5	14,600	Moderate	0
2	F	63	Diffuse	Plasma Cell	All Red Marrow	9.2	4.1	9	3.5	5.7	1.2	14,900	Heavy	0
3	M	61	Solitary then Multiple	Plasma Cell	Vertebrae and Flat Bones	12.6	3.7	6.8	.	1.7	1.7	250	Trace	0
4	F	59	Solitary then Multiple	Plasma Cell	Vertebrae	18	2.0	6.5	4.8	1.7	3.5	14,000	Trace	0
5	M	15	Solitary then Multiple	Plasma Cell	Vertebrae	11.1	4.2	.	.	1.7	38	8,400	Heavy	+
6	F	32	Solitary then Multiple	"Myeloid"	Femurs Ilium	4.4	..	17,000	Trace	0
7	F	12	Multiple Focal	"Myeloid"	Femur Skull	10.3	4.1	.	.	3.8	.	10,000	0	0
8	M	62	Multiple Focal	"Myeloid"	Flat Bones	.	.	9	.	2	..	8,400	Trace	0
9	F	68	Multiple Focal	Plasma Cell	Vertebrae Pelvis	0
10	M	40	Multiple Focal	Plasma Cell	Flat Bones	11	4.8	7.5	.	2.4	7,700	Heavy	Not Examined	0
11	M	55	Multiple Focal	"Myeloid"	Flat Bones	10.5	7.2	.	.	2.8	7,900	Heavy	0	0
12	F	16	Multiple Focal	"Myeloid"	Flat Bones	11.1	3.7	6.0	3.7	2.8	2.7	20,000	Moderate	0
13	F	36	Multiple Focal	"Myeloid"	Ilium Skull	.	.	8.1	4.9	3.2	4.3	7,200	0	0



FIG. 1.—An X-ray film of the lumbar spine of a patient with the uncommon solitary focal type of bone demineralization. There is a spherical defect in the body of the second lumbar vertebra.



FIG. 2.—An X-ray film of the lumbar spine of a patient with diffuse myelomatous changes. There is loss of structure of the vertebral bodies and bony architectural deformations. The appearance may be mistaken for fracture, osteoporosis.

8 it was severe enough (from 1.2 to 2.8 million r.b.c.) to constitute an outstanding sign. Leucocytosis, young myeloid forms and Türk cells which are sometimes found in the peripheral blood are produced in other diseases which affect the marrow, probably the result of irritation. All but 3 in our series showed these phenomena. An increase in the sedimentation rate was found in the 3 cases in which the test was made. This is probably a non-specific reaction, since the sedimentation rate is increased in hyperglobulinemia.

If the myeloma process is a solitary lesion a needle biopsy may give tangible evidence of its true nature. Needle biopsies of bone are not as difficult as most clinicians seem to believe and in the case of the myeloma where there is Roentgen-ray guidance and cortical destruction they are particularly easy. A positive diagnosis was made on the only one of our series on which it was tried. In such instances the usual aspiration needle may be used but it is possible to get through a rather heavy compacta with a needle of the Turkel type. The tumor cells, if properly treated, are not difficult to interpret by the pathologist because of their distinctive morphology.

BONE LYSIS. While pathological fracture is given in most accounts as the most constant sign of the disease,⁸ bone pain almost invariably occurs first, and if properly interpreted a much earlier diagnosis can be made. It is quite true, as pointed out by Geschietter, that pathological fracture of a flat bone is apt to mean destruction by myeloma because most other osteolytic processes are more likely to involve cylindrical bones, but back or chest pain with focal tenderness almost invariably precedes the fracture by months. It may be argued that the symptom of back pain is so common in the myeloma age group that it is almost worthless as a diagnostic aid, but, if patients with this symptom were thoroughly studied from the outset, it would mean in almost every instance an economy of money and time for both patient and physician. Nine of

our patients complained of back pain as the initial and outstanding symptom and the other four gave a history of pain in the affected bone.

In many instances a Roentgen-ray film of the involved skeletal part will suggest the diagnosis of bone destruction by malignant neoplasm. An original diagnosis was so made in 5 of our series, and in only 2 cases did the first roentgen examination fail to reveal presence of bone disease. The Roentgen-ray cannot always define the cell type of the tumor, but such a diagnosis points the way to further laboratory study which should eventually fix the correct nature of the lesion. It is unfortunate that in a certain number of myeloma cases the demineralization is so diffuse that unless the radiologist and clinician are aware of this possibility a diagnosis of osteoporosis may be made. Two of our 13 cases were so classified. On one of these the diagnosis of diffuse myeloma was made later by biopsy and the other came to necropsy before the true nature of the disease was suspected. With the complaint of flat-bone pain and a Roentgen-ray description of generalized demineralization, the clinician must not be satisfied with a diagnosis of senile osteoporosis until sternal marrow smears have been examined and other diagnostic laboratory procedures performed.

If the tumor is of the generalized type which produces this picture in the majority and perhaps in all cases, a marrow smear, usually from the sternum, may present myeloma cells. This procedure is so simple that one wonders why it is not universally applied where myeloma is suspected. If the diagnosis of diffuse myeloma cannot be sustained, then other causes of generalized demineralization may be considered. These are carcinomatosis, hyperparathyroidism (rare), osteomalacia (rare in this country), osteoporosis secondary to renal insufficiency, osteoporosis due to hyperthyroidism, rarely tuberculosis or Gaucher's disease and finally idiopathic senile osteoporosis.

In conclusion it should be emphasized that an early diagnosis of myeloma can be made if the symptoms of bone pain are considered sufficient reason for Roentgen-ray study. If focal or generalized demin-

eralization is so demonstrated, the diagnosis can be made or ruled out by marrow smear and study of the blood and urine. As a last resort aspiration or open biopsy may be tried on a focal lesion. Cases of

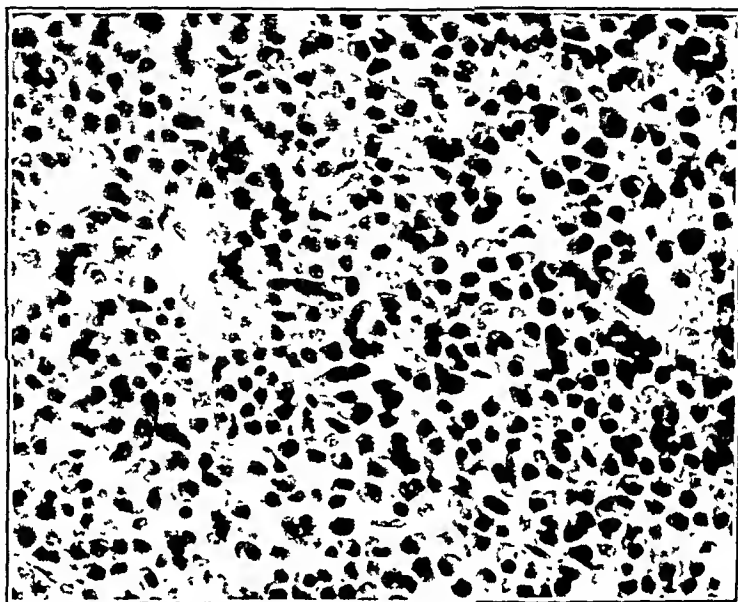


FIG. 3.—The usual or "classical" plasma cell type of multiple myeloma. Some cells are typical plasmacytes. Others appear to be young forms of the same type.

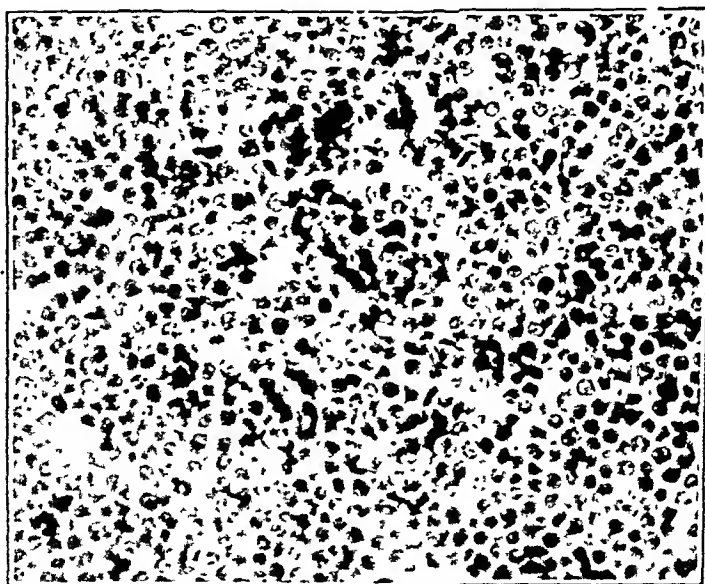


FIG. 4.—Atypical type of multiple myeloma. The cells show greater basophilic cytoplasm. None of the cells can be identified as plasmacytes.

generalized demineralization should not be diagnosed as idiopathic senile osteoporosis until these studies have been carried out.

Summary. There are four main points which need emphasis in considering myeloma of bone.

1. There are three clinical subtypes: that which begins as a single focus, but eventually becomes multiple; the classical multicentric tumor; and the diffuse type which involves all the red marrow simultaneously. The rare extra-medullary type acts quite differently and should not be included in this group.

2. Myeloma is a group of tumors of which the plasma cell is only one type. They all arise from marrow elements and they all behave similarly.

3. Severe back pain or persistent bone pain of obscure origin warrants Roentgen-ray examination. If demineralization is found, there are a number of laboratory procedures which are helpful in establishing a diagnosis of myeloma. The urine should be examined for signs of renal disease and Bence-Jones protein. The blood should be analyzed for increased globulin. A sedimentation rate may be helpful. Sternal marrow should be aspirated and examined for myeloma cells.

4. It should be remembered that all the marrow may be involved diffusely, and so a patient with evidence of generalized bone demineralization should not be dismissed with a diagnosis of idiopathic senile osteoporosis.

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DISSEMINATED CALCIFICATION OF THE PANCREAS: SUBACUTE AND CHRONIC PANCREATITIS

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THE purpose of this paper is to draw attention to the least frequently recognized form of pancreatic lithiasis, known variously as disseminated calcification of the pancreas, pancreatitis petrificans and diffuse parenchymal calcification of the pancreas, and to add two reports of cases to those now existing in the literature. An attempt will also be made to stress the clinical picture which should aid in its more frequent recognition in the future, to suggest the relation of the condition to other forms of pancreatitis, and to discuss its treatment.

It was Beling³ who first suggested, in 1940, that a distinction should be made between disseminated calcification of the pancreas and the usual form of pancreatic lithiasis. In the former condition he suggested that a variable portion of the parenchyma of the gland is replaced by calcium deposits and in the latter the ducts contain single or multiple stones. He collected 12 cases of calcification of the pancreas from the literature, and credits Allen² with describing the first in 1903. From a study of this group, and an additional case of his own, Beling describes a clinical picture and a characteristic history.

King and Waghlstein⁴ reported four additional cases in 1942; one additional patient each is reported by Pascucci,⁵ Sage,⁶ and Thannhauser⁷ and 2 by Wechsler and Weimer,⁸ bringing the total number of cases in the literature prior to this report to 22. While the patients described by the two last mentioned authors were not classified as disseminated calcifi-

cation of the pancreas, but simply as pancreatic lithiasis, we feel that the symptomatology, laboratory studies and Roentgen-ray findings are sufficiently typical to warrant reclassification.

The incidence of pancreatic lithiasis in general is not high. The aggregate figures from ten pathological laboratories showed only 31 cases among 117,031 routine necropsies or 0.044%.⁸ However, the reliability of these statistics is questioned by the work of Ludin⁷ who, after a preliminary roentgenogram of the pancreas at post-mortem, dissected all the glands showing heavy shadows and demonstrated stones in 28 out of 542 organs, or 5.5%.

ETIOLOGY. The cause of disseminated calcification of the pancreas is not known but is thought to result from repeated attacks of acute or subacute pancreatitis occurring in adult life. Consequently the theories regarding the etiology of acute pancreatitis, such as bile regurgitation, infection or metaplasia of the ducts with consequent obstruction, are equally applicable here. It seems to us that it may also be possible that this condition is the result of chronic pancreatitis originating in childhood. Since disseminated calcification of the pancreas has been found to occur in patients as young as 17 years, symptoms frequently date back to childhood and the characteristic features of abdominal pain, weakness, malnutrition, icterus and steatorrhea are common to both. Cole and Howe⁹ describe a similar syndrome occurring in patients with pancreatic atrophy associated with fatty degeneration of the

liver and claim this syndrome is similar to that found in children with chronic cystic fibrosis of the pancreas.

PATHOLOGY. Detailed pathologic studies of the pancreas in cases of disseminated calcification are not numerous. The majority of patients in whom this condition has been diagnosed have not had histologic section of the pancreas made; instead, the diagnosis was made by gross examination of the gland at operation or autopsy, or as a result of roentgenogram. Grossly the gland is firm, showing beneath the capsule numerous fine, hard, white bodies. Upon cutting, these are noted to be calcareous deposits, and the finer ducts are dilated and seen to contain minute calculi removable with a needle. Those cases in which histological examination has been made showed the presence of extensive inter- and intra-lobular fibrosis and considerable mononuclear cell infiltration. The parenchyma of the gland was largely replaced by this fibrosis, and those acinar cells remaining were normal in appearance except in those areas where there was marked intra-lobular fibrosis. When the fibrosis is particularly extensive it may encroach upon, and replace, the islet cells, but usually these remain intact in spite of the wide-spread acinar replacement. The larger ducts show a variable degree of dilatation and minute calculi are seen to extend from here through the smaller ducts and into the finest acini; however, they do not appear to impinge upon or replace the actual secreting cells.

In 6 of the 15 patients with disseminated calcification of the pancreas who were operated upon or observed at necropsy, stones were found in the larger ducts in addition to the calcification present in the parenchyma. It would seem likely that the diffuse gritty sensation observed on cutting into the gland and the diffuse infiltration noted upon Roentgen examination might be the result of very fine radicles of the pancreatic ducts being almost completely filled with deposits of finely granular calcium salts. If this is true it would suggest that the deposition of calcium is

simply a progressive phase of the condition causing the deposit of pancreatic calculi in the larger ducts. However the outstanding histologic feature is the marked interlobular fibrosis and the atrophy or replacement of acinar tissue. In this respect there is marked similarity in the histology of this disease to that of the pancreatic atrophy of Cole and Howe's patients and chronic cystic fibrosis in children.

SYMPTOMATOLOGY. In the 24 reported cases there were 20 males and 4 females; 22 of whom were white and 2 colored. The average age was 38.6 years; the youngest patient was aged 17 years and the eldest 76.

The outstanding symptom of which these patients complain is some form of abdominal pain, usually existing over a period of months or years. In some patients the onset of symptoms could be traced back to childhood. The pain varies greatly in severity and location. It is usually of a gnawing, boring type, occasionally described as knife-like. It is most frequently present in the epigastrium, going through to the back, but may also radiate to the right or left hypochondriac regions, the pelvis or either shoulder. The episodes of pain may vary considerably in length, and are usually not related to meals. However, particularly severe attacks may arise following an excessive intake of alcohol. Nausea, bloating, anorexia and vomiting are frequently present. The pain may be relieved by taking sodium bicarbonate but more frequently it requires morphine. Steatorrhea and cretorrhea are present in about 25% of the patients. When this exists for any length of time, weakness and loss of weight may be pronounced. In the 24 cases reported transient jaundice with enlargement of the liver was present in 8 cases; diabetes in 2 cases; in 9 cases a history of excessive indulgence in alcohol was obtained; 3 patients had an associated pulmonary tuberculosis and 3 had syphilis.

LABORATORY FINDINGS. The most important laboratory finding is an absent or

diminished pancreatic secretion. It is now generally felt from the work of Agren and Lagerlof,¹ that considerable information regarding pancreatic function can be obtained from the secretin test.

This is carried out by introducing a specially designed double-lumened tube into the stomach and duodenum, which permits aspiration of the gastric and duodenal secretions simultaneously. When a basal level of duodenal juice is obtained the secretin is injected intravenously. Normally there is a prompt increase in the volume of the juice and in its bicarbonate and enzyme content. A marked reduction in volume and in bicarbonate and enzyme content is indicative of abnormal pancreatic function. There are other methods of stimulating the pancreatic secretion, such as injecting mechohyl, which stimulates the vagus and thereby increases the enzyme content but has little effect on the volume; and the introduction of hydrochloric acid or ether⁴ into the duodenum is thought by some to cause an increase in the pancreatic secretion similar to that produced by secretin but of less intensity. We have employed the latter method because secretin was not available commercially and the untoward side effects that occur at times with mechohyl made us feel that this procedure was contraindicated in an already sick or weakened patient.

STOOL EXAMINATION. If steatorrhea is present the stool grossly is large, mushy and formless; if collected in a pan and allowed to stand for a while the free fat will separate and run off in small streams. The odor is fetid, but there is not much frothing or bubbling of gas; the color is light tan, and glistens due to the fat. Microscopically a great increase in oil droplets is readily discernible, and staining with Sudan III brings this out strikingly. Creatorrhea, or the presence of striated muscle fibers in the feces, is characteristic and easily recognized in simple wet microscopic preparations. Chemical analysis for total fat will show a considerable increase over the normal amount, but

further analysis for the partition of neutral fat and fatty acids hardly seems to aid much in differential diagnosis since it is now generally recognized that free fat can be eliminated in the stool both in diseases of disturbed intestinal absorption and pancreatic insufficiency.

URINALYSIS. Routine urinalysis shows little when the condition is primary, but during acute episodes and in the presence of marked wasting a variable degree of albuminuria may develop.

BLOOD COUNT. This ordinarily shows a normal number of leukocytes and a slight normocytic anemia, but during acute episodes there may be a moderate leukocytosis.

BLOOD CHEMISTRY. This likewise varies little; the serum amylase is usually within normal limits, but may be elevated during an acute episode; the blood cholesterol is low normal or at times definitely reduced, and blood sugar is normal.

In patients who have developed a secondary diabetes, glycosuria and a typical diabetic curve in a glucose tolerance test will be obtained.

LIVER FUNCTION TEST. When jaundice is present it is usually mild. The available data show that the qualitative van den Bergh reaction is positive direct and the quantitative reaction shows a slight elevation. There may be some retention of bromsulfalein and an increase in the alkaline phosphatase activity.

ROENTGEN EXAMINATION. The typical Roentgen picture in disseminated calcification of the pancreas shows a diffuse, stippled calcification involving the head, body and tail. This has been observed to take place within an 18-month period in 1 case, and in another a progression has been observed beginning in the head, going through the body and reaching the tail within 7 years. While the finding of typical calcification of the pancreas on Roentgen-ray examination, when the condition is advanced, will rarely permit of misinterpretation, it should be borne in mind that the degree of calcification may be minimal and not necessarily in propor-

tion to the severity of the symptoms. In addition, unless a plane film of the abdomen is made, the calcification of the pancreas that is present may be obscured by the materials used in conducting some other examination such as a gastrointestinal series, cholecystogram, barium enema or pyelogram. Even if the calcification is noted upon Roentgen-ray examination it may be looked upon as a coincidental finding and no importance attached to it; it should be stressed that with such Roentgen-ray finding, although symptoms are minimal and not attributed to pancreatic dysfunction, the possibility of the future development of symptoms is great. Additional Roentgen-ray findings that may be of aid in evaluating this condition are the typical deficiency pattern of the small bowel described by Golden and the granular appearance of the small bowel contents resulting from a mixture of feces and free fat.

DIAGNOSIS. In any patient with a long history of upper abdominal pain the possibility of disseminated calcification of the pancreas should be considered. Subsequent confirmation of the diagnosis is then dependent upon: (1) a plane film of the abdomen including that area between the 1st and 4th lumbar vertebrae; (2) stool examination for total fat and steatorrhea and (3) pancreatic function test.

It should be borne in mind that this condition may simulate many other chronic diseases of the abdomen but that the character of the pain is usually of a gnawing, boring type, going through to the back, frequently on the left. When the roentgenogram, stool examination, and pancreatic function test are carried out there will usually be found definite roentgenographic evidence of calcification in the abdomen, steatorrhea, and steatorrhea in the stool and a reduction in the pancreatic secretion, if disseminated calcification of the pancreas is present.

The disease with which this condition is most commonly confused is some form of biliary tract disturbance, usually cholecystitis. However, if the character of the

pain, and the long history, frequently going back to childhood, are kept in mind, pancreatic involvement will be diagnosed more frequently. Differentiation should be able to be established by carrying out the studies referred to above.

Similarly, peptic ulcer is another lesion that gives rise to symptoms in the right upper quadrant; both pancreatitis and ulcer are associated with nausea and vomiting and pain that may be relieved with alkalis. However, the pain associated with the pancreatic lesion is not so rhythmical, is less related to food and is usually located on the left side, as well as on the right. The presence of occult blood in the stool, gastric analysis and gastrointestinal Roentgen-ray should be sufficient to diagnose the ulcer.

Perforated viscus may be suspected when the patient is having a particularly severe attack of pain; the recti muscles may be extremely hard and vomiting and prostration pronounced. If there is an accumulation of air under the diaphragm diagnosis will not be difficult, but in its absence differentiation may not be possible until the acute symptoms have subsided.

Renal lesions are apt to be suspected if the pain extends into the pelvis or follows down one of the ureters; this is more apt to occur on the left as a result of the tail of the swollen, enlarged pancreas coming into contact with the ureter. Hematuria and left lumbar pain are in favor of the renal involvement, but the absence of pyuria or renal calculus should stimulate further search for the cause.

TREATMENT. The relief of the acute symptoms usually requires the administration of morphine, while simple sedatives and rest will carry the patient through the milder attacks. When the condition is far advanced and a true pancreatic insufficiency is established causing steatorrhea, weakness and cachexia, it can be benefited by a low-fat, high-caloric diet, vitamins and large doses of Pancreatin. Vitamins A and D would appear to be indicated because of the failure of absorption that existed during the pancreatic

deficiency state. Pancreatin should be given in triple strength in enteric-coated pills, and the dosage should be gauged according to the response in weight gain and the reduction in steatorrhea. In some patients 8 gm. daily has been recommended to accomplish this.

Although there has been surgical removal of stones in the larger ducts of the pancreas associated with disseminated calcification, there is no evidence that this has materially changed the course of the disease. Recently partial and total pancreatectomies have been performed in selected patients with intolerable pain and threatened morphinism. The extent of

pancreatic removal was the extent of involvement of the organ with calculi and calcification.¹³

We wish to describe 2 patients with disseminated calcification of the pancreas; the first we diagnosed during his latest admission. The second patient was not seen by us but was included because it is the only other instance of this condition that we could find after a search of the clinical, pathologic and Roentgen-ray files at the hospital.

Case Reports. CASE 1. F. A., white, male, aged 33, occupation, miner. We first saw this patient when he was admitted to the hospital in February, 1946, at which time

TABLE 1.—LABORATORY FINDINGS IN CASE 1, F. A.

Admission	First	Second	Third	Fourth	Fifth	Sixth
Hemoglobin	94%	71%	70%	45%	79%	90%
RBC.	4,200,000	3,200,000	3,500,000	2,500,000	3,500,000	4,100,000
WBC	13,600	4,000	10,000	11,400	14,200	6,300
Wassermann	negative		negative	negative	negative	negative
Urinalysis:						
Albumin	one plus	negative	two plus	negative	negative	negative
Sugar	negative	negative	negative	negative	negative	negative
Stool Examination.					positive for occ. blood No excess fat, ova or parasites present	1. Many fat globules. 2. Fat 42% dried wt. 3. Fat 23% dried wt. 4. Fat 18% dried wt.
Retention of Bromsulfalein	none			10%	none	none
van den Bergh:						
Qualitative	negative			positive	negative	negative
Quantitative (mg. per 100 cc.)	0.3			1.7	0.6	0.4
Urobilinogen			positive 1-50	.. .	
Cholesterol (mg. per 100 cc.)	94			366	124	158
Ester (mg. per 100 cc.)	62			288	104	121
Free (mg. per 100 cc.)	32			78	20	37
Protein (gm. per 100 cc.)	6.76		6.14		6.65	5.8
Albumen (gm. per 100 cc.)	3.83		3.64		4.81	3.5
Globulin (gm. per 100 cc.)	2.93		2.5		1.84	2.3
Urea Nitrogen:						
BUN (mg. per 100 cc.)	8.95			9.8
NPN (mg. per 100 cc.)	18		29	22	
Prothrombin time				100%	.
Serum Amylase	less than 80 units
Gastric Analysis:						
Total acid	57 units					45 units
Free acid	41 units					25 units

Glucose Tolerance Curve (Sixth Admission).

Fasting: 126 mgs. %; 1st hr. 147 mgs. %; 2nd hr. 85 mgs. %; 3rd hr. 60 mgs. %; 4th hr. 65 mgs. %; 5th hr. 77 mgs. %; 6th hr. 72 mgs. %.

he was complaining of an upper respiratory tract infection, abdominal pain and diarrhea. We found that he had been admitted on 5 previous occasions during the past 7 years, with complaints of upper abdominal pain.

His first admission was on March 19, 1939. His past medical history revealed that he had had no serious childhood illnesses; his appendix was removed in 1934; he had a soft chancre which was treated as syphilis, in 1938 and in November, 1938, he had a

cholecystectomy for "hydrops of the gall-bladder" at another hospital. This latter operation was complicated by a post-operative atelectasis. For many years he had been a heavy drinker, consuming a pint to a pint-and-a-half of whiskey daily.

At the time of this admission the patient was complaining of upper abdominal pain radiating through to the right shoulder blade, intermittent nausea and vomiting for the past nine months. During this time he had



FIG. 1.—Case 1. Roentgenogram showing the progression in pancreatic calcification from 1939 to 1946



FIG. 2.—Case 1. Roentgenogram showing small bowel deficiency pattern.



FIG. 3.—Case 1. Roentgenogram showing granular appearance of ileum due to mixture of free fat and feces.

had some diarrhea and lost 50 pounds in weight. He had previously had constipation for a "long time." The patient states that these complaints were not relieved by the cholecystectomy in 1938, in fact he thinks they were aggravated.

Upon physical examination the patient did not appear to be acutely ill. The only positive finding was tenderness upon deep palpation in the right upper quadrant. The liver was enlarged and tender and the edge fairly smooth and sharp. A cholecystogram, taken because there was some doubt as to whether the gallbladder had been removed, showed no evidence of biliary calculi, but calcification was noted in the right upper quadrant just adjacent to the body of the first transverse process. This same calcification was again noted upon two additional Roentgen examinations. Exploratory laparotomy was performed and a large mass was found firmly adherent to the under side of the liver, from which several loops of small bowel were dissected. The great thickness of the adhesions was thought by the surgeon to be due to a suppurative process following the cholecystectomy. The pancreas was noted to be hardened in its entirety. Postoperatively the patient developed a sub-hepatic abscess which was drained. He recovered and was discharged from the hospital on June 15, 1939.

During the succeeding 2 years the patient was re-admitted to the hospital on 4 separate occasions at intervals varying from 1 to 7 months. The symptoms of which he complained during this time were similar to those he had upon his first admission, namely, a gnawing, boring pain in the epigastrium, radiating through to the back, which was not related to food, and only relieved by opiates, nausea, vomiting and loss of weight.

On the first of these admissions he was treated symptomatically; on the next admission there were clinical and Roentgen findings suggestive of pyloric obstruction for which a gastroenterostomy was done. On the third admission transient jaundice was present and thought to be due to a stone in the common duct which had passed, and on the fourth admission, because of the patient's continued complaints without demonstrable organic cause, a psychiatric consultation was held and a diagnosis of constitutional psychopathic state was made.

In April, 1944, he was operated upon at another hospital for a herniated intravertebral disc.

On February 2, 1946, 5 years after his last admission, he was admitted for the sixth time, with a primary complaint of upper respiratory tract infection of 3 weeks' duration. In addition, for the past 18 months he had been having intermittent attacks of sharp, colicky peri-umbilical pain radiating to the left flank, groin, scrotum and inner aspect of the thighs. These attacks occurred about once every 2 to 3 months and lasted about 2 weeks. During the attacks, and with heavy coughing, vomiting was frequent. The patient states he often induced vomiting which relieved the nausea and partially relieved the pain. For the past 2 or 3 years he had been having 11 to 12 stools daily. These frequently followed meals and contained undigested food and oily liquid. Physical examination revealed dry, wheezing and coarse, crackling râles throughout both lung fields, and the liver was enlarged three fingers' breadth below the costal margin. The temperature was 101.4 F., there was no icterus and no abdominal tenderness. Microscopic stool examination showed many fat globules and undigested striated meat fibers. The chemical analysis showed fat to be 42% of the dried weight. On 2 pancreatic function tests, no trypsin was present in any of the fractions obtained following stimulation with ether. The absence of pancreatic trypsin was confirmed on August 16, 1946, in a secretin test performed by one of us (W. J. S.) and Dr. M. H. F. Friedman. The volume response was within normal range but no trypsin was detected in any of the duodenal drainage samples.

A gastrointestinal Roentgen-ray revealed no evidence of abnormal lesion in the upper gastrointestinal tract except for moderate changes indicative of small bowel deficiency pattern and a granular appearance that was thought to be due to an admixture of free fat and the barium. A roentgenogram of the abdomen revealed diffuse calcification of the pancreas, and one of the chest showed accentuated hilar shadows with increased pulmonary markings radiating to both bases.

On bronchoscopic examination there was edema and redness of the bronchi and the presence of thick, tenacious mucus was noted.

On the basis of the calcification and the

small bowel pattern seen upon Roentgen-ray examination, the steatorrhea and creatorrhea, and the absence of trypsin, a diagnosis of disseminated calcification of the pancreas with pancreatic insufficiency was made.

Treatment was instituted by giving the patient a low-fat diet, vitamins A and D, and Pancreatin. Initially 15 grains of Pancreatin were given daily, but it was only after this was increased to 90 grains daily

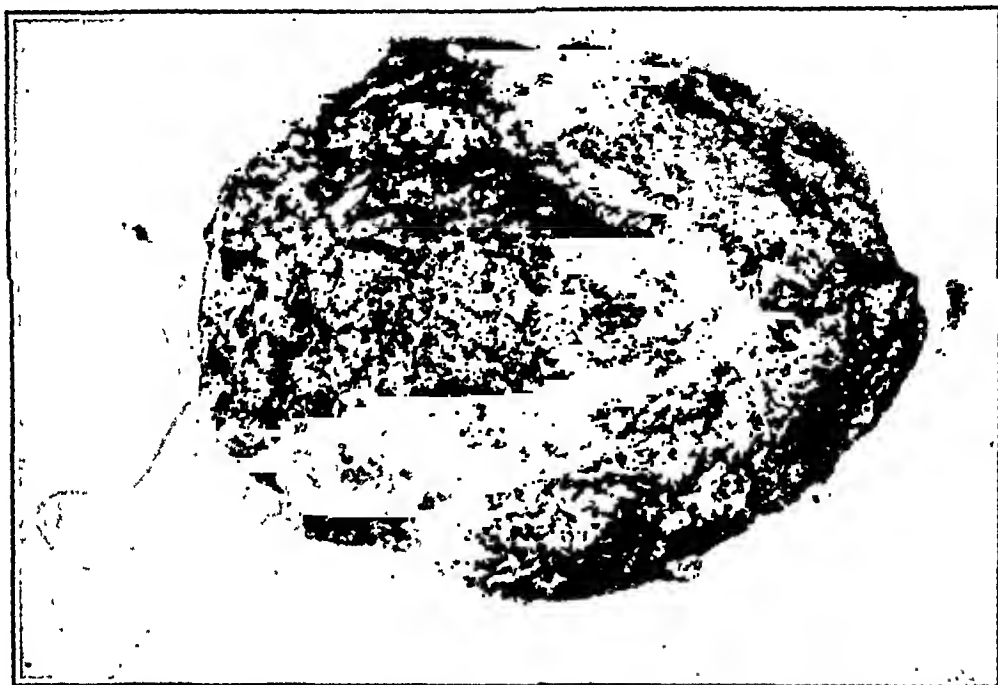


FIG. 4.—Case 1. Stool showing typical steatorrhea. Note oily liquid flowing freely about margin of stool.

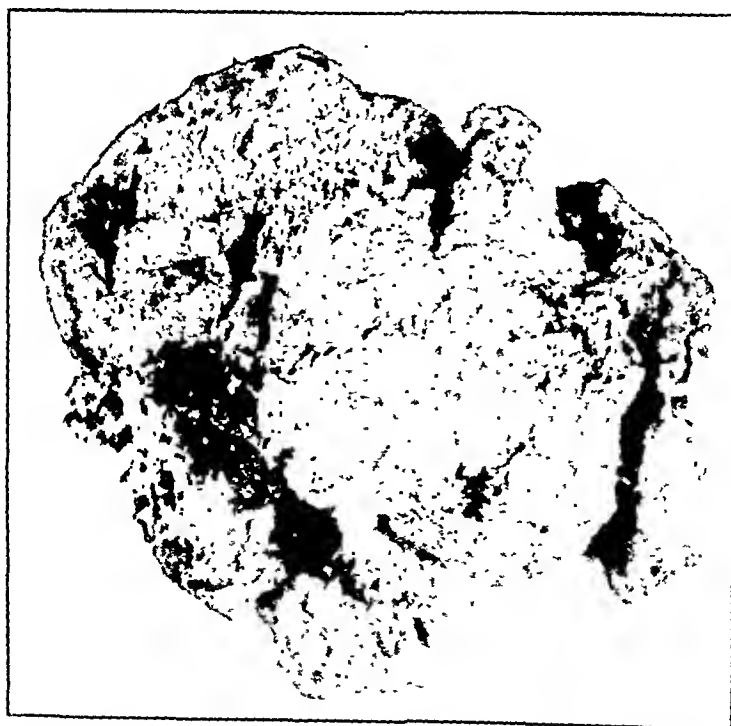


FIG. 5.—Case 1. Appearance of stool after two weeks' therapy.

that there was a substantial reduction of fat in the stool and an increase in the patient's weight.

On this regimen he made steady progress. The number of stools dropped from 11 or 12 to 1 or 2 daily. They remained bulky and formless but grossly they were free of excess fat and no longer fetid. He felt generally better, his appetite improved and he gained 13 pounds in weight, but was not completely free of mild attacks of abdominal pain. However, these attacks were distinctly less intense in character and of shorter duration than those he had previously experienced. The general improvement was sufficient to permit his discharge from the hospital and he was advised to return to the out-patient clinic for further follow-up.

pain disappeared. During one of these episodes he noticed that his skin was slightly yellow.

Except for the abdominal pain referred to above, the only relevant finding in his personal history was that he indulged heavily in alcohol. Upon admission the physical examination was essentially negative except for moderate tenderness and muscle guarding over the gallbladder region and in the right flank. No icterus was present. The temperature was 101.8 F. which dropped slowly to normal within 3 days.

Hemoglobin was 78%, erythrocytes 3,900,000 per cu. mm. The blood prothrombin time was 44% on August 4th and 82% on August 12th. The serum amylase was 88 units, and the plasma protein was 5.8 gm.



FIG. 6.—Case 2. Roentgenogram showing extensive calcification of the pancreas.

The laboratory findings on this patient for all admissions are summarised in Table 1.

CASE 2. E. K., white, male, aged 47. Occupation, elevator operator. This patient was admitted to the hospital on August 13, 1943, complaining of right upper quadrant pain which had been recurring at irregular intervals over a period of nine years. It was colicky in nature and penetrated through to the back beneath the right scapula. With each recurrence the initial phase was so severe that morphine was required to give relief and he would then follow a restricted diet for a variable period of time until the

On August 4th the qualitative van den Bergh reaction was negative direct and quantitative 1.3 mg. per 100 cc., and on August 12th there was still a negative direct reaction and serum bilirubin was 0.2 mg. The urea clearance was 73% of average normal. A routine urinalysis was negative except for 1-plus albumin.

A cholecystogram showed a normally functioning gallbladder without evidence of calculi, but the presence of extensive calcification of the pancreas was noted.

A Roentgen-ray picture of the chest revealed prominent hilar shadows in both lung

fields and minimal tuberculosis in the left second intercostal space.

The patient was given bed-rest and treated symptomatically; the pain subsided slowly over a period of 9 days and he was discharged symptom-free on August 19, 1943, with a diagnosis of acute cholecystitis which had subsided.

Since this patient was not re-admitted, an attempt was made to trace him through his former employer and we learned that he had died in June, 1945, in a Veterans' Tuberculosis Sanitarium. Unfortunately no autopsy was performed and there were no records available indicating that any further pancreatic dysfunction had been recognised. Nevertheless, on the basis of the long history of repeated attacks of severe abdominal pain, the transient mild jaundice and the presence of marked, diffuse calcification of the pancreas seen upon Roentgen-ray examination, we felt that this patient represented an additional case of disseminated calcification of the pancreas.

Comment and Conclusion. Probably one of the greatest benefits that will accrue from the proper recognition of this disease is that it may prevent the needless removal

of a gallbladder, appendix or kidney. As has been demonstrated in one of our patients the erroneous removal of his gallbladder led to a series of operations to overcome the sequels of the first, without in the least benefiting the condition giving rise to the initial symptoms. On one occasion, due to the persistent complaint of abdominal pain for which no organic cause could be found, this patient was also diagnosed as a psychoneurotic. That this error has occurred previously is indicated by the paper of Yaskin¹⁴ who reported 4 cases of pancreatic disease in 1931 in whom a diagnosis of functional disturbance was made, and by that of Riekles⁹ who in 1945 added 3 cases with depression and anxiety as the presenting symptom. Both authors emphasize that the clinician should always be on guard to rule out disease of the pancreas when deep-seated pain in the epigastrium is associated with mental symptoms. Remaining alert to the possibility of the existence of disseminated calcification of the pancreas in a patient is probably the most important single factor in its recognition.

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EXPERIENCES WITH PENICILLIN AND DICUMAROL IN THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS*

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ALMOST simultaneously in March, 1943, it was reported in both the United States¹³ and England¹¹ that during treatment of subacute bacterial endocarditis with penicillin the blood was freed of green-producing streptococci, but that the infection recurred after the withdrawal of penicillin. This concept persisted throughout 1943. In January of 1944, Loewe and his associates¹⁵ reported on 7 consecutive cases in which the use of penicillin and the simultaneous administration of the anticoagulant heparin had proved successful.

This was the status of our knowledge when penicillin became more readily available for civilian use in June of 1944. A few earlier attempts had been made at the State of Wisconsin General Hospital to treat subacute bacterial endocarditis with the new drug. Varying quantities of penicillin were used and the treatment was carried on for various periods of time. Because at that time an anticoagulant seemed to have definite value, it was decided to use Dicumarol in combination with penicillin. Dicumarol, 3,3'-methylenebis (4-Hydroxycoumarin), had been identified by Professor K. P. Link and his associates^{7,8,14,24} as the toxic factor in spoiled sweet clover and was later isolated and crystallized by them. It had been used clinically by Meyer et al.^{2,19} and Allen et al.⁶ as an anticoagulant. After having used heparin and the sulfonamides in the treatment of subacute bacterial endocarditis, Allen¹ at the Mayo Clinic substituted Dicumarol, but fatal cerebral hemorrhages occurred as they had with the former combination of heparin and sul-

fonamide. Experiences with our early cases have been reported in two previous papers^{18,25}.

One year after the report of Loewe, however, Dawson and Hunter⁹ published their results with two series of cases, in the first of which they used a combination of penicillin and heparin and in the second penicillin alone. The results in the two series were equally favorable. The experience of Bloomfield³ in California and of Katz²⁰ in Chicago also indicated that the anticoagulant was unnecessary. The reports which continue to appear in the literature^{16,21,23} indicate that at least 50% or more of unselected cases are arrested.

There is a marked difference of opinion as to the optimum length of time that therapy should be continued. Bloomfield, et al.^{3,4,5} lean toward prolonged therapy, a view which we share¹⁸. Meads, Harris and Finland¹⁷, on the other hand, obtained comparable results with therapy of no more than 2 weeks' duration, and similar findings are reported by Hunter and Dawson¹⁰ who found intensive courses over relatively short periods of time to be effective. The method of administration is also in question. Bloomfield and his group⁴ lean toward interrupted intramuscular injections in the majority of cases, as we do also; Goerner and Blake¹² favor the continuous intravenous route, and Dawson and Hunter¹⁰ feel that their best results are obtained by continuous intramuscular injections.

Methods. In general, penicillin was administered only to patients from whom at least 2 positive cultures had been obtained.

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The organism was checked in vitro to determine its sensitivity to penicillin, by a method similar to that of Thomas, Levine, and Vitagliano²⁶; drops of various concentrations, namely, 0.05, 0.25 and 0.5 units per cc., were placed in small wells on an agar plate and the resulting zone of inhibition was noted. A suitable method for clinical administration was developed early. By the time 3 or 4 cases had been treated certain broad principles had been evolved. Six weeks was decided upon as the shortest period of time in which organization of vegetations could be expected and penicillin administration was carried on for at least that long. As penicillin was still relatively scarce, it was given intramuscularly in 6 daily doses for a total of 120,000 units. Later, with added experience, and more penicillin available, we concluded that this dosage should be increased, and treatment was started with an intramuscular injection of at least 25,000 units every 3 hours. Intramuscular administration being the most convenient, was utilized in all cases unless the patient did not respond and a trial by another route seemed indicated. In several refractory cases we later administered 1,000,000 to 3,000,000 units of penicillin daily by continuous intramuscular or intravenous drip. Dicumarol was administered in an initial dose of 4 or 5 mg. per kilogram. Subsequent daily doses of 1.5 mg. per kilogram were given to maintain a prothrombin time between 25 and 50% of normal, as determined by Pohle and Stewart's²² modification of the Quick method. In the first trials Dicumarol was begun shortly after the initiation of penicillin therapy. After the death of a patient (Case No. 9) following a few days of combined therapy, possibly from cerebral hemorrhage, it was decided to begin Dicumarol therapy only after the temperature became 99 or less or after the cultures became negative. Penicillinase was not used in the culture media in this study, and this was probably responsible for suppression of many otherwise positive blood cultures. The patients were, however, kept in the hospital for 5 to 14 days after treatment was finished and cultures were taken every day or two during this time. The first check-up examination was usually advised at the end of one month, at which time most of the relapses were obvious.

Results. Thirteen cases were treated with penicillin and Dicumarol (Table 1). Of this group, 11 had rheumatic valvular lesions, 1 had a congenital lesion, and 1 was believed to have a combined congenital and rheumatic lesion. Seven recovered and remained well for intervals of 10 to 17 months. The duration of symptoms before therapy was begun ranged from 1 to 17 months, the average being $3\frac{1}{2}$ months. After therapy was initiated, fever usually subsided by the 14th day, the average being $12\frac{1}{2}$ days. In all but one case cultures became negative in 1 to 3 days; in that case it took 27 days. The average length of time that elapsed before negative cultures were obtained was $5\frac{2}{3}$ days. The smallest total dosage administered in these successful cases was 2,500,000 units and the largest 20,200,000. Only 2 of these patients had received penicillin therapy previously. The blood cultures of all were positive for *Streptococcus viridans*, and all of the organisms were sensitive to penicillin in vitro, giving inhibition with 0.05 unit per cc. We include the summary of one of these successful cases.

Case Reports. CASE 3. A 24-year-old white male entered the hospital on August 23, 1944. In May he had had "grippe" with chills, fever, and backache. Sulfonamide therapy gave temporary relief for approximately a week, after which the symptoms recurred. Past history revealed that at the age of 9 he had had rheumatic fever. Physical examination showed that the patient was acutely ill, and scattered petechiae were noted. The heart showed signs of a double aortic lesion. The spleen was barely palpable. There was mild anemia, and 3 cultures were positive for *Streptococcus viridans*, sensitive to penicillin, with a zone of inhibition of 25 mm. around a drop containing 0.05 unit per cc. On September 1, 1944, penicillin in quantities of 35,000 units every 4 hours injected intramuscularly was started along with Dicumarol. On September 16 penicillin was reduced to 25,000 units every 4 hours, on the 30th to 20,000 units, and on October 4th to 15,000 units. It was discontinued completely on October 12th. The initial fever in this case was 105.8 degrees F.

and by the second day of therapy it had decreased to 99. The first negative blood culture was obtained on September 2nd. The course was uneventful and he was discharged on October 19, 1944. A subsequent check-up in March of 1945 revealed that there had been no recurrence of symptoms, and 3 negative cultures were obtained. On March 29, 1946, there was still no evidence of recurrence.

Another patient (Case 8) had a relapse after almost a year, during 7 months of which he had been working. He had had a tooth extracted and had been given what was erroneously thought to be adequate prophylactic penicillin therapy. Penicillin was given 14 hours before and 54 hours after the extraction in quantities of 15,000 units every 3 hours. Within a week, however, he again had chills and fever, and positive cultures for *Streptococcus viridans* were obtained. He was under therapy from June, 1945, to February, 1946, but the condition was not arrested. He is

being treated again and will be the subject of a separate report.

Of the 5 unsuccessful cases in this group, 3 relapsed promptly after the discontinuance of therapy. Two of these (Cases 11 and 13) had received previous penicillin therapy in inadequate doses and the third (Case 12) left the hospital against our advice before completing the minimum 6 weeks' course which we had advocated. These 3 have made recoveries on penicillin therapy alone in massive doses and case summary No. 11 follows.

CASE 11. A 21-year-old white male had been a patient here in January of 1944. At that time a diagnosis of subacute bacterial endocarditis with rheumatic mitral stenosis and insufficiency had been made. Sulfamerazine and typhoid vaccine gave temporary improvement. He returned on May 23, 1944, and cultures were persistently positive for *Streptococcus viridans*. He had a gnawing abdominal pain, nausea, and hematemesis and was placed on a modified Sippy regimen. Subsequent studies of his gastro-intestinal

TABLE 1.—CASES TREATED WITH PENICILLIN AND DICUMAROL

Case No.	Discharge Date	Age Yrs.	Duration of Symptoms	Organism	Previous Therapy	Penicillin Units Total Dosage	Fever to	Days After Rx.—99°	First Negative Culture after Rx.	Course
Case 1 N.E.W.	8-30-44	38	6 mo.	Strep. viridans	0	2,500,000	102 ²	1 day	1 day	Arrested.
Case 2 J.G.W.	8-31-44	40	2 mo.	Strep. viridans	0	3,185,000	104 ¹	14 days	2 days	Arrested.
Case 3 R.M.	10-19-44	24	3 mo.	Strep. viridans	0	6,300,000	105 ⁸	1 day	1 day	Arrested.
Case 4 G.W.	12-19-44	39	4 mo.	Strep. viridans	+	6,000,000	101 ²	19 days	2 days	Arrested.
Case 5 F.K.	3-5-45	33	4 mo.	Strep. viridans	+	20,200,000	102	36 days	2 days	Arrested.
Case 6 B.R.	3-20-45	48	3 mo.	Strep. viridans	0	8,535,000	102 ²	12 days	27 days	Arrested.
Case 7 D.K.	3-31-45	16	1 mo.	Strep. viridans	0	7,095,000	101	2 days	3 days	Arrested.
Case 8 J.R.	8-19-44	48	5 mo.	Strep. viridans	0	4,295,000	103	6 days	4 days	Relapse. 1 yr. after dental extraction.
Case 9 G.W.	10-12-44	33	7 mo.	Strep. viridans	+	720,000	103 ²	Never	Never	Died — Possible cerebral hemorrhage.
Case 10 D.D.	2-7-45	40	7 mo.	Strep. viridans	+	12,805,000	101 ⁶	Never	Never	Died.
Case 11 L.M.W.	2-7-45	21	17 mo.	Strep. viridans	+	23,760,000	101	7 days	Never	Arrested after 42,000,000 intensive.
Case 12 R.J.S.	7-5-45	22	2 mo.	Strep. viridans	0	4,960,000 6,385,000	103	6 days	2 days	Arrested after 52,914,000 intensive.
Case 13 J.F.S.	8-27-45	39	6 mo.	Non-hemo. strep.	+	8,360,000	100 ⁴	2 days	41 days	Arrested after 20,840,000 intensive.

tract, including Roentgen-ray, esophagoscopy, and gastroscopy, failed to reveal the source of this trouble. Penicillin became available at this time and he was given 1,100,000 units, starting June 27, 1944, and after 1 week on this therapy his temperature was normal and the cultures were negative. He was discharged on July 10, 1944. When he returned on October 2, 1944, the blood cultures were again positive, and combined therapy, 25,000 units of penicillin every 4 hours intramuscularly and oral Dicumarol, was instituted. This was gradually reduced and toward the end of a course of 11,860,000 units, 5 negative blood cultures were obtained. He was discharged on December 20, 1944. He was admitted once more on February 7, 1945, when cultures were again positive. Penicillin was given in quantities of 50,000 units every 3 hours for a total of 23,760,000 units along with Dicumarol. The temperature, which had been 101 on admission, fell to normal a week after therapy was begun. On March 28, 1945, he had another hematemesis, and at this time Dicumarol was stopped. Again diagnostic studies were negative. He recovered rapidly from this episode and was discharged at his request on June 5, 1945. All cultures during this stay were positive. On July 10, 1945, after having another hematemesis, the patient returned. He was now given 1,000,000 units of penicillin daily in 1,000 cc. of glucose as a continuous intravenous drip. No Dicumarol was given. The therapy was continued for 42 days. Only 1 culture (on August 10, 1945) was positive. He was discharged on August 24. When seen in check-ups on September 26 and November 27, 1945, and on March 26, 1946, he was getting along well, and the 9 cultures taken at these times were negative.

The 2 cases which were complete failures include a 40-year-old white female (Case 10), with a *Streptococcus viridans* organism sensitive to penicillin in quantities of 0.25 unit per cc., who was under therapy for almost 4 months. She had previously received 2 short courses of penicillin elsewhere consisting of 2,500,000 units and 3,000,000 units respectively, each of which given over a 10-day period resulted in temporary relief of symptoms. She received penicillin here in quantities as high

as 25,000 units every 2 hours, intramuscularly, and for a time part of the daily dosage was given by the continuous intravenous route. A total of 12,805,000 units was given. During her entire stay she ran a septic type of fever, and cultures were persistently positive. The last case (Case 9) had a *Streptococcus viridans* organism which was resistant to the action of penicillin, and she apparently died of a cerebral hemorrhage following initiation of the combined therapy, though autopsy was not permitted.

Nine patients received penicillin alone, 8 of whom had rheumatic lesions and 1 a possible combined congenital intraventricular septal defect and rheumatic mitral and aortic disease (Table 2). Two of these were in the group before our organized plan was established. In others Dicumarol was withheld because negative blood culture and control of fever were not obtained. Two others are in the group because anticoagulant therapy seemed contraindicated. Of the total group of nine, 4 died and came to autopsy, and the following findings were noted. The first (Case 17) was a 76-year-old white male who received 15,000 units of penicillin every 4 hours intramuscularly for a total of 810,000 units. At autopsy an ulcerated vegetation was noted on the mitral valve, which showed previous rheumatic damage. There were many bacterial colonies and no evidence that the vegetation was healing. Splenic infarctions were also present. The second (Case 18) was a 46-year-old white male who had previously received inadequate therapy. He was given 3,420,000 units in approximately 11 days in quantities as high as 50,000 units every 3 hours, intramuscularly. He developed a pulmonary infarction and died. Autopsy revealed that the aortic valve was involved, and though it was obvious that repair had proceeded, with fibroblastic activity and some calcification, this did not counterbalance the destructive process and a few "puny" colonies were seen. The third case (Case 19) was the first patient to receive penicillin for subacute

bacterial endocarditis at this hospital. He was 51 years old and had had a total of 2,000,000 units intramuscularly, 15,000 units every 4 hours, for 22 days; and at the time of his discharge from this hospital, cultures were negative. Approximately 5 months later he developed congestive heart failure and died at another hospital. At that time cultures were negative. Autopsy showed organized lesions on the valves, but scattered colonies of bacteria were present in the organized tissue. The last case (Case 20) is described in some detail because of the findings on the heart valve when autopsy was performed.

excursion. The heart was enlarged, systolic aortic and mitral murmurs were noted. There was abdominal distention, tympany, and marked tenderness, especially in the right upper quadrant with muscle spasm and rebound tenderness. The liver was 4 cm. below the right costal margin. Laboratory studies showed a hemoglobin of 8 grams, red blood cell count of 2,860,000, white blood cell count of 11,200 with 90% neutrophils. A urinalysis showed 0.07% albumin with clumps of white blood cells. A fluoroscopic examination substantiated the fact that the right leaf of the diaphragm was not moving. The impression was subphrenic abscess and bilateral pyelonephritis, and after several transfusions a surgical ex-

TABLE 2.—CASES TREATED WITH PENICILLIN

Case No.	Discharge Date	Age Yrs.	Duration of Symptoms	Organism	Previous Therapy	Penicillin Units Total Dosage	Fever to	Days After Rx.—99°	First Negative Culture after Rx.	Course
Case 14 C.L.P.	7-1-44	13	1 mo.	Type V Pneumo.	0	2,160,000	105 ⁴	18 days	2 days	Arrested.
Case 15 S.G.	11-4-44	33	7 mo.	Strep. viridans	0	5,860,000	102	2 days	2 days	Arrested.
Case 16 V.A.K.	12-5-45	31	2 mo.	Strep. viridans	+	26,475,000	102 ⁴	2 days	17 days	Arrested.
Case 17 P.D.L.	6-22-44	76	½ mo.	Strep. viridans	0	810,000	105	Never	Never	Died.
Case 18 E.S.	7-23-45	46	4 mo.	Strep. viridans	0	3,420,000	104 ⁸	Never	9 days	Died.
Case 19 J.I.	7-11-44	51	11 mo.	Strep. viridans	0	2,000,000	103 ²	13 days	1 day	Died — Congestive heart failure.
Case 20 J.A.K.	11-8-44	30	2 mo.	Non-hemo. strep.	0	1,250,000	103 ⁴	Never	1 day	Died — Congestive failure & complications.
Case 21 J.H.N.	1-20-45	39	1 mo.	Strep. viridans	+	180,000	102 ²	1 day	Never	Died.
Case 22 G.K.	6-29-45	20	5 mo.	Strep. viridans	+	31,900,000	103	Never	Never	Died.

CASE 20. A 30-year-old white female entered the hospital on September 19, 1944, as an emergency case; she had severe pain in the right upper quadrant, abdominal distention, nausea, vomiting, chills, and fever. Symptoms had begun 5 weeks previously, had become progressively more severe; during this time there had been a 25-pound loss of weight. She had had similar complaints prior to a cholecystectomy in 1935. On physical examination she appeared pale and acutely ill; respirations were rapid and shallow and the fever was 101. There were a few basal rales in the right lung, the right diaphragm was elevated and there was no

ploration for possible drainage of the subphrenic abscess was made. About 500 to 800 cc. of clear yellow fluid were removed, and a liver biopsy showed subacute to chronic hepatitis. A cystoscopic examination later confirmed the diagnosis of pyelonephritis on the right due to *B. Aerogenes* and on the left due to *Streptococcus fecalis* and *B. Pyocyaneus*. While in the hospital her course continued to be stormy; she developed petechiae and after several negative blood cultures one was obtained which was positive for a nonhemolytic streptococcus. Sulfadiazine had been of no avail and with the positive culture a tentative diagnosis of

subacute bacterial endocarditis or periarteritis nodosa was made and penicillin was given, 15,000 units every 4 hours for a total of 1,250,000 units. In spite of this therapy, nausea and vomiting became marked and the patient died on November 18, 1944. An autopsy was performed, which showed subacute bacterial endocarditis with small vegetations on the aortic and mitral leaflets, splenic infarctions with rupture of one into the subphrenic space, renal and liver infarction, rheumatic endocarditis, chronic pericarditis and myocardial infarction. Besides this, periarteritis nodosa was present. The description of the valve is worthy of note. The aortic leaflet showed a small vegetation 0.5 mm. in diameter. The mitral leaflet had one small adherent vegetative area 2 mm. in diameter. On microscopic examination there was hyalinization of the vegetations which were completely sterile. The subacute bacterial endocarditis appeared to be healed.

Three of the cases described above had fairly large lesions. The finding of colonies on an organized valve, as in Case 19, has been previously reported by Bloomfield⁴. The complete healing of Case 20 is of interest. This might have occurred without therapy in the natural course of the disease. On the other hand, since the vegetations were small, therapy may have been adequate in this case.

Of the remaining cases which did not receive Dicumarol, one, a 33-year-old white female, was 5 months pregnant and stated at the time of admission that she had vaginal bleeding. She also had jaundice thought to be due to cholecystitis and cholelithiasis. She responded to penicillin therapy alone. Two other patients did not receive Dicumarol, one because the prothrombin time was low on admission (Case 14, a *Type V Pneumococcus* infection) and the other (Case 16 with a *Streptococcus viridans* organism present) because he had had a stormy course before therapy was started. The 2 remaining cases have died, one in the hospital of a convulsion after receiving only 160,000 units, the other at home, her symptoms never having come under control in spite

of 31,900,000 units, part of which dosage was administered in combination with sulfadiazine for 7 days, and part of it by the constant intravenous drip.

Hence, in the entire group of 13 cases that received the combined therapy, 8 were arrested, 1 of these relapsed after a year, 3 additional cases recovered on later regimens of intensive penicillin therapy alone. Of 9 treated with penicillin alone, 4 were arrested, 1 of these died and sterile healed vegetations were noted at autopsy, and another with negative cultures 5 months after therapy showed colonies still present in the vegetation at autopsy. Fifteen absolute arrests were obtained in the total series of 22 cases.

We noted that the early cases in our series were easily controlled, whereas later we encountered more that were refractory and there was difficulty in getting the patients under control. We got the impression that this occurred after penicillin became more readily available for civilian use and that a larger number of cases had been subjected to inadequate therapy before coming under our observation. We therefore analyzed our cases as to previous penicillin therapy during the course of the illness (Table 3). Ten of the patients had received previous penicillin therapy, a number of them in large doses for a short period of time. One other had undergone an interrupted course of therapy. All but one of these had improved temporarily with the initial therapy received elsewhere. Of this group 3 died before completion of our therapy and 2 other cases never came under control. Of the remaining 6, one had a drop in temperature in 2 days and a negative culture on 30,000 units every 3 hours, and one became normal in 3 days on 40,000 units every 3 hours, a third on 1,000,000 units daily in 8 days. But the others had fever for 20 to 28 days and the average period of fever for the group was $16\frac{1}{6}$ days, as compared with $8\frac{1}{3}$ days for those who had received no previous therapy. In cases previously untreated, cultures became negative on an average of $4\frac{2}{3}$ days after initiation of therapy, as

compared with $11\frac{1}{2}$ days in cases that had had previous therapy. A conclusion as to the significance of this point is not justified, but it may be highly significant. No explanation has presented itself, since in all but one of these cases the organism was still sensitive *in vitro*.

In this group of 22 cases, 13 had petechiae on entrance to the hospital. In only 2 of these did petechiae persist throughout treatment, despite freedom from fever and negative blood cultures. In these 2 cases, cultures became positive 1 or 2 weeks after the discontinuance of therapy. When the patients were later subjected to regimens that were to prove effective, embolic phenomena did not occur.

Comment. It is difficult from this series to decide upon an optimum dosage of penicillin. When we started the study, the quantities utilized obviously gave adequate blood levels for only a short time, yet these cases included our greatest number of successes. On the whole the organisms were rather sensitive to penicillin, and it seemed that adequate levels for 1 hour out of 3 or 4 was sufficient. This follows closely the findings of Bloomfield and Halpern⁵, who were able to control 3 of 4 cases treated with 4 injections daily of 50,000 units each. We agree with these authors that very large doses are probably unnecessary in the ordinary case. In our Cases 11, 12 and 13, however, which were

refractory, intensive therapy undoubtedly was responsible for their arrest.

The difference in favor of combined penicillin and Dicumarol therapy is not as significant as it would seem, since after the first 4 cases only those that were responsive to penicillin received Dicumarol. It is especially significant that 3 of the most refractory cases which did not respond to doses of 8,360,000 units, 23,760,000 units and 11,345,000 units of penicillin respectively when it was combined with Dicumarol did later respond to total doses of 20,840,000 units, 42,000,000 units and 52,940,000 units administered without Dicumarol. We are, therefore, decidedly skeptical that any benefits are to be derived from anticoagulant therapy, which certainly carries with it grave hazards in subacute bacterial endocarditis. Penicillin therapy, however, has given decidedly better results than anything previously available.

The need for sensitivity tests was apparent from the start, and there was good correlation between sensitivity of the organisms and clinical response. In the early cases the levels of penicillin in the blood were not obtained because of the lack of technical aid. In our recent cases, however, we have been making these determinations, and they are of definite value in regulating the dosage, especially in the refractory cases. There is no clear cut

TABLE 3.—COMPARISON OF CASES WITH AND WITHOUT PREVIOUS PENICILLIN THERAPY

NO PREVIOUS THERAPY				PREVIOUS THERAPY			
Case No	Total Dosage Units	Days After Rx.—99 ^o	First Negative Culture	Case No	Total Dosage Units	Days After Rx.—99 ^o	First Negative Culture
1	2,500,000	1 day	1 day	4	6,000,000	19 days	2 days
2	3,185,000	14 days	2 days	5	20,200,000	36 days	2 days
3	6,300,000	1 day	1 day	11	42,000,000	18 days	29 days
6	8,535,000	12 days	27 days	13	20,840,000	3 days	2 days
7	7,095,000	2 days	3 days	12	52,914,000	2 days	20 days
8	4,295,000	6 days	4 days	16	26,475,000	28 days	17 days
14	2,160,000	18 days	2 days				
19	2,000,000	13 days	1 day				
15	5,860,000	2 days	2 days				
Average	4,658,888	7 $\frac{2}{3}$ days	4 $\frac{2}{3}$ days		28,071,366	17 $\frac{2}{3}$ days	12 days
		Patients who died before therapy was completed					
17	810,000			9	720,000		
20	1,250,000			21	1180,000		
				10	12,805,000		
				22	31,900,000		
				18	3,420,000		

evidence that it was more difficult to treat patients with long-standing symptoms than those with more recent symptoms. It is probable, however, that the size of the vegetation as well as the extent of destruction to the heart valve contributes to the refractory nature of some cases. Case 20, if she had active lesions at the time first seen, emphasizes this point. The presence of colonies of organisms in the valve in Case 19 likewise brings up a point previously noted by Bloomfield⁴. This may later be the source of a recurrence, or hyalinization and calcification may become so complete that the focus is walled off.

Summary and Conclusions. Of 22 patients with subacute bacterial endocarditis, 13 received both penicillin and Dicumarol, and 9 were given only penicillin. From our experience to date, we have acquired certain impressions and tentative conclusions:

1. Treatment with penicillin alone or where combined with Dicumarol should be persistent for a minimum of 6 weeks.

2. This prolonged therapy has given decidedly better results than anything previously employed.

3. Despite our results favoring combined therapy, we remain decidedly skeptical that antieoagulant therapy offers any advantages and it is unquestionable that antieoagulant therapy carries with it grave hazards in subacute bacterial endocarditis.

4. Penicillin therapy for 54 hours after removal of a focus of infection is *inadequate* to prevent the development of subacute bacterial endocarditis.

5. It was noted that patients who had received distinctly inadequate therapy before coming under observation presented a more difficult problem as far as control was concerned. Five of 7 failures were in this group. All but 1 of the inadequately treated patients had become subjectively and objectively improved under the original penicillin therapy. We raise the question as to the possible great significance of this point and although a final conclusion regarding it is not justified, it may be important.

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THE TREATMENT OF ACUTE DIPHTHERIA AND THE CHRONIC CARRIER STATE WITH PENICILLIN*†

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SINCE the introduction of antitoxin by Behring,³ no other agent capable of exerting a specific effect in infections due to *Corynebacterium diphtheriae* has been discovered. The modern treatment of diphtheria, therefore, is directed entirely towards neutralization of circulating toxin. The causative organisms are not affected primarily by the method of treatment in use and are eradicated from the focus of infection mainly through the activity of the normal tissue defense mechanisms.

The sulfonamides have been found to exert little effect against the organism of diphtheria. Examination of the *in vitro* susceptibility of *C. diphtheriae* to penicillin by Fleming,^{6,7} Chain et al.,⁵ Abraham et al.,¹ and by Herrell¹⁰ have shown that this bacterium is susceptible to the antibiotic agent. Heilman⁹ established fatal infections in both guinea pigs and hamsters with the gravis strains of *C. diphtheriae* and administered penicillin in quantities usually effective against the organisms but failed to protect either of these experimental animals against the infection. Four cases of nasal and faucial Klebs-Loeffler bacillus infection were treated by Turner¹⁵ with nasal drops containing 250 units of penicillin per cc., given every 3 hours for 48 hours, with the resultant clearing of the organism from the mucous membrane in 24 hours.

Twelve patients who had diphtheria due to the gravis strain were treated by McSweney¹² with both intramuscular injections and throat and nasal spray of

penicillin in doses of 202,500 to 750,000 units. Four of the individuals died. The antibiotic agent was thought to produce more rapid subsidence of the faucial edema and "bull neck" and to hasten clearing of the diphtheritic membrane. Nose and throat cultures did not reveal *C. diphtheriae* as long as penicillin spray and nose drops were used. The author concluded that between 700,000 and 800,000 units of penicillin were necessary in the treatment of Grade 3 and 4 diphtheria.

In spite of the fact that a large number of different agents and procedures have been examined for their effect on the carrier state in diphtheria, very little progress has been made in the development of an efficient method for eradication of *C. diphtheriae* from the noses and throats of healthy individuals who harbor them. Very little work has been done on the treatment of diphtheria carriers with penicillin, and only 4 reports have been found in the literature on this subject. Large amounts of penicillin were administered intramuscularly to diphtheria carriers from 1 to 2 weeks by Peterson, Northrop, and Herrell.¹⁴ In a few cases, negative cultures were obtained at the time the antibiotic agent was administered or shortly after therapy had been completed. "However, there were recurrences." Ber-
man and Spitz⁴ treated 10 proven diphtheria carriers by the instillation of 1 cc. of solution containing 500 units of penicillin 4 times each day for 5 days, and immediately after each nasal instillation,

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spraying the fauces and the posterior wall of the pharynx with 1 cc. of the same solution. They reported a reversion to a non-carrier state within a period of 5 days. Eight of the cases were followed for 4 weeks and were found to remain free of the Klebs-Loeffler bacilli.

Treatment with 300,000 units of penicillin per day by the intramuscular route was reported by Koehler and Siemsen¹¹ to be without influence on the diphtheria carrier state. When lozenges containing 500-1,000 units of the antibiotic agent were administered to patients hourly for 12 doses over a period of 3 to 15 days, and, in addition, nasal sprays of the drug were given every 2 hours, 74% of the cases showed eradication of the diphtheria bacilli from the nose and throat. Tonsillectomy produced clearing of the organisms in those individuals in whom no results were obtained with penicillin lozenges and sprays. Paull, Tucker, Holladay, and Nieewonger¹³ were unable to show any effect on the diphtheria carrier state by penicillin in the nebulized state.

The purpose of the work reported here was to examine the effect of penicillin on the clinical course and bacterial flora of the nose and throat in acute cases of diphtheria, and to determine the value of the drug in the chronic diphtheria carrier state.

Methods. All patients admitted to the hospital with a diagnosis of acute diphtheria or of the carrier state were subjected to a complete physical examination in which special attention was paid to the characteristics of any membrane present in the nose or pharynx. Cultures of both the nasal and pharyngeal mucosa, carried out immediately after entry to the hospital and daily thereafter until the patient was discharged from the hospital, were inoculated on heart-infusion-tryptose-yeast-blood-agar and tellurite agar. After incubation for 24 to 48 hours at 37° C., all suspicious colonies were stained with either Mallory's acid methylene-blue, or Loeffler's alkaline-methylene-blue and examined microscopically. In addition, all of

the strains isolated were typed either in our own laboratories or in those of Dr. Howard Mueller of the Department of Bacteriology of the Harvard Medical School. Three times a week, cultures of the pharynx and nose were sent to the Massachusetts State Department of Health for confirmation. All strains of *C. diphtheriae* isolated from carriers were examined for virulence, and no case from which virulent organisms were not recovered was treated.

Penicillin was administered intramuscularly in a dose of 15,000 to 30,000 units every 3 hours for an average of 12 days after the diagnosis of acute diphtheria or the carrier state had been established bacteriologically; in about one-third of the cases, larger amounts of the drug were given. All of the patients with acute infection received an adequate quantity of diphtheria antitoxin. Electrocardiograms were taken frequently and physical examination of the heart and nervous system carried out daily in order to detect the onset of myocarditis or polyneuritis. All patients were followed clinically and bacteriologically for a minimum of 2 weeks after penicillin treatment had been stopped; in some cases, the follow-up period was as long as 2 months.

Results. I. Cases of Acute Diphtheria. Thirty-eight cases of diphtheria involving various portions of the upper respiratory tract were treated with antitoxin alone or with antitoxin plus penicillin.

Twelve patients were given only diphtheria antitoxin. Their ages ranged from 5 to 43 years (average, 18.5), and they had been ill with signs and symptoms of diphtheria for from 2 to 8 days before admission to the hospital. In 8 of the individuals, the disease was confined to the pharynx, in 1 it involved both the nose and pharynx, in 1 the pharynx and larynx, and in 2 was limited to the nasal mucous membrane. All of the patients were found to be infected with the mitis strain of *C. diphtheriae* and were given between 5,000 and 60,000 units of diphtheria antitoxin intramuscularly and/or

intravenously. Eleven had an uncomplicated clinical course and 1 developed acute myocarditis. Studies of the time required for the diphtheria organisms to disappear from the nose and pharynx revealed that in one instance *C. diphtheriae* was not recoverable 5 days after antitoxin had been given. In the other 11 cases, between 17 and 75 days were required for eradication of the Klebs-Loeffler organism; in 2 individuals, the organisms disappeared after 18 days, and in 2 after 30 days. In 1 instance each, the *Corynebacteria* could be recovered up to the 10th, 17th, 25th, 47th, 51st, 73rd, and 75th days after antitoxin treatment. The average time required for disappearance of *C. diphtheriae* in this group of patients was 33.25 days.

Twenty-six cases of acute diphtheria were treated with penicillin in addition to antitoxin. The ages of the individuals in this group varied between 2 and 65 years (average, 21.4) and they had been ill for 2 to 11 days (average, 4.75 days) before admission to the hospital. Distribution of the diphtheritic lesions was as follows: In 21, the pharynx alone was involved, in 2 the pharynx and nose, in 1 the pharynx and larynx, and in 2 the pharynx, larynx, and nose. These patients were all infected with the mitis strain of *C. diphtheriae* and received between 20,000 and 80,000 units of antitoxin by the intramuscular and/or intravenous route (average, 32,000 units); in addition, they were given varying amounts of penicillin. The first three cases were treated with 120,000 units of penicillin per day for slightly less than 3 days (total, 330,000 units). When this quantity was found to be ineffective, the dose was increased to 120,000 to 240,000 units a day for approximately 12 days. Two individuals in this group suffered from complications of diphtheria; one, who had received only 330,000 units of the drug, had severe myocarditis with heart failure and peripheral neuritis. Another, who had been given larger quantities of penicillin, developed polyneuritis with strabismus in the second week of

his illness and weakness of all the extremities and complete areflexia 4 weeks later.

From 60 to 70 days were required before the cultures of the throat and pharynx became negative for *C. diphtheriae* in the 3 patients who received only 330,000 units of penicillin. In the 23 individuals given the larger doses of the antibiotic agent, the diphtheria bacillus disappeared from the nose and throat of 9 in 3 days, of 5 in 4 days, of 2 in 5 days, of 3 in 1 day, and of 1 patient each in 2, 7, 8, and 14 days, respectively. Negative cultures were obtained in 17 of the 23 cases (73.8%) in 4 days or less. The average time required for this group to become free of the Klebs-Loeffler bacillus was 3.96 days when the 3 cases receiving the smaller dose of penicillin were omitted from the calculation.

In order to conserve space, the individual histories and detailed data of each case have been omitted and the results summarized in Table 1.

II. Diphtheria Carriers. Ten individuals, ranging in age from 2 to 44 years, who had been proven carriers of virulent diphtheria bacilli for varying periods of time and were sent to the hospital because of board of health regulations requiring their quarantine, received no treatment after admission. Cultures of the nose and pharynx taken at frequent intervals revealed a very slow rate of disappearance of the organisms from these 2 sites. In 5 patients, *C. diphtheriae* persisted for 19, 38, 43, 49, and 52 days, respectively. Two cases were allowed to leave the hospital 54 days after admission, at which time they still harbored the Klebs-Loeffler bacteria. Two children who were siblings of a case of acute pharyngeal and laryngeal diphtheria were subjected to tonsillectomy and adenoidectomy 90 days after they had been discovered to be diphtheria carriers; 1 week after operation, nose and throat cultures were still positive.

Thirteen chronic carriers of *C. diphtheriae*, ranging in age from 3 to 40 years, were treated with penicillin. The first 2 individuals studied received only small

amounts of the drug, but thereafter, the total quantity administered was increased to 1,000,000 units or more. When 120,000 units of the antibiotic agent were given every day for 12 days (total, 1,440,000 units), the time required for the Klebs-Loeffler bacilli to disappear was between 3 and 30 days, but over 50 % of the patients retained the organisms for fairly long periods of time. Since this amount of penicillin appeared to produce only slow clearing of the carrier state, the quantity of the drug was increased to

2 days and could not be demonstrated at any time in the following 2 weeks.

All of the patients were followed clinically and bacteriologically at frequent intervals for a period varying from 8 to 45 days after penicillin treatment was stopped, the cultures being examined in 2 laboratories simultaneously.

The results of treatment of diphtheria carriers with penicillin are presented in Table 2.

Discussion. No striking alteration could be detected in the clinical course of cases

TABLE 1.—SUMMARY OF RESULTS OBTAINED IN THE TREATMENT OF DIPHTHERIA WITH PENICILLIN

Number of Cases	Antitoxin—No Penicillin	Type of Treatment
	12	Antitoxin Plus Penicillin 26
Age	5-43 years (Average—18.5 yrs.)	2-65 years (Average—21.5 yrs.)
Locations of Diphtheritic Lesion	Pharynx, 8 Pharynx and Nose, 1 Pharynx and Larynx, 1 Nose, 2 All cases—mitis type	Pharynx, 21 Pharynx and Nose, 2 Pharynx and Larynx, 1 Pharynx, Larynx and Nose, 2 All cases—mitis type
Type of <i>C. diphtheriae</i>	5,000—60,000 (Average, 40,000)	20,000—80,000 (Average, 31,350)
Dose of Antitoxin (units)		
Amount of Penicillin given during entire course of treatment (units)	0	3 cases—330,000 23 cases—1,440,000—2,290,000
Complications	Myocarditis—1 case	Myocarditis and polyneuritis—1 case Polyneuritis—1 case
Time required for disappearance of <i>C.</i> diphtheriae from nose and pharynx	17-75 days (Average—33.25 days)	3 cases receiving 330,000 Units of Penicillin—60-70 days (Average—66.6 days) 23 cases—1-14 days (Average—3.96 days)

240,000 units per day for 12 days. The administration of the larger dose resulted in the eradication of *C. diphtheriae* in 3 to 4 days.

Two carriers, 1 of whom had received 1,440,000 units of penicillin in 12 days, another 2,760,000 units in 23 days, remained positive for 45 and 35 days, respectively. The first patient was re-treated with 3,120,000 units in 12 days and showed complete eradication of *C. diphtheriae* from the pharynx and nose in 3 days. The second individual was given the same quantity of penicillin as in the first course of treatment but this was injected over a period of only 9 days instead of the original 23 days. With this treatment, the organisms disappeared in

of acute diphtheria which received penicillin in addition to antitoxin when compared with those given antitoxin alone. The outstanding difference between the 2 groups was a marked reduction in the time required for the causative organism to disappear from the pharynx and nose in those treated with penicillin. Although the number of patients studied was too small to draw any conclusions concerning the effect of penicillin therapy on the incidence of complications, the drug seemed to be of little value in this respect.

The time required for *C. diphtheriae* to be eradicated from patients who were treated with antitoxin alone varied between 17 and 75 days (average, 33.25 days), while in those treated with peni-

cillin, excluding those receiving less than 1,000,000 units, it ranged between 1 and 14 days (average, 3.96 days).

The question may be raised as to whether 3.96 days may not be within the normal time necessary for clearance of diphtheria bacilli from infected individuals treated with antitoxin alone and that

thought that the rate at which convalescent carriers ceased to harbor organisms was a direct function of the number of surviving positive carriers at any time, and that the disappearance of the bacilli from the pharynx followed the following

simple logarithmic law: $\frac{\log n_1 - \log n_2}{t_2 - t_1} = k$,

TABLE 2.—SUMMARY OF RESULTS OBTAINED IN THE TREATMENT OF DIPHTHERIA CARRIERS WITH PENICILLIN

Name	Age	Penicillin No. of Days Given	Total Dose— Units	Time Required for <i>C. diphtheriae</i> to Disappear from Nose and Pharynx (days)	Follow-Up Period (days)
J. V..	23	7	540,000	9	10
W. S..	8	3	240,000	11	8
L. M..	2	13	1,240,000	13	14
B. K..	30	14	1,300,000	12	16
H. F..	9	13	1,440,000	30	14
V. M..	3	14	1,680,000	21	30
L. L..	40	9	1,080,000	3	21
M. W..	22	12	1,440,000	3	21
V. M..	13	12	1,440,000	5	21
C. L..	10	12	2,880,000	4	21
D. G.—First Treatment	20	23	2,760,000	23*	12
D. G.—Second Treatment	20	9	2,840,000	2	14
J. Q.—First Treatment	12	12	1,440,000	12†	45
J. Q.—Second Treatment.	12	12	3,120,000	3	21
A. A..	16	12	3,120,000	2	14

* Cultures became negative in 23 days and then became positive again.

† Cultures became negative in 12 days and then became positive again.

the average of 33.25 days observed in those not receiving penicillin was unusual. A review of the literature on this subject reveals that the data obtained with reference to the time of disappearance of *C. diphtheriae* in individuals treated with penicillin are probably significant. Andrews, Bulloch et al² state that, in general, a large number of cases of diphtheria lose the bacilli within a "few days" of the disappearance of the membrane and that the remainder gradually develop negative cultures; abnormal cases, however, may persist as carriers for many months. A careful study of the persistence of the causative organism in 450 cases of diphtheria was made by Hartley and Martin⁸ who found that about 75% of the patients still harbored the bacteria 7 days after admission to the hospital, 67% showed positive cultures after 10 days, 50% after 14 days, and 30% after 21 days. It was

where n_1 and n_2 equal the number of individuals still carrying the organism at times t_1 and t_2 . The results obtained indicated that about 5% of the surviving positive convalescents became negative each day.

Weaver¹⁶ made a similar study of 500 cases and found that about 93% still carried *C. diphtheriae* at the end of 7 days, 72% after 14 days, and 43% after 21 days. He concluded that there was approximately a 9% decrease in the carrier rate each day.

A study of the rate of disappearance of the Klebs-Loeffler bacillus from the nose and pharynx of patients with acute diphtheria was made by Wright,¹⁷ who analyzed his data on the basis of type of organisms producing the disease. Of individuals infected with the mitis strains, 56% were still positive after 7 days, 44% after 14 days, 36% after 21 days, 27% after 28

days, and then gradually decreasing numbers so that after 70 days, 4% still harbored the bacteria.

When the figures reported by Wright¹⁷ are averaged, it is found that about 19.3 days was the mean time required for *C. diphtheriae* to disappear from the pharynx and nose. An analysis of 130 cases of diphtheria admitted to the Haynes Memorial Hospital over a period of several years and treated only with antitoxin revealed that an average of 19.1 days elapsed before the organisms disappeared. Although the value, 33.25 days, observed in the present study, is somewhat high as compared with the data present in the literature, this may be so because of the small number of cases analyzed. It seems very probable, however, on the basis of the findings of the present study as well as those that have been published in the literature with respect to patients treated with antitoxin alone, that the percentage of individuals free of diphtheria bacilli within 4 days after becoming ill is very low. The average time of 3.96 days for clearance of *C. diphtheriae* from patients treated with antitoxin and penicillin appears to be very significant, therefore, and seems to make tenable the conclusion that treatment with penicillin is very effective in shortening the carrier state in the acute stage of diphtheria.

The investigations reported here did not confirm the reports in the literature that the chronic diphtheria carrier state persists for only about 10 days, or Weaver's observation that about 40% of carriers become negative after 7 days, 65% after 20 days, and 87% after 40 days. A fairly large number of patients who were carriers of *C. diphtheriae* for periods ranging be-

tween 4 and 5 months were observed in the present study; in several instances, tonsillectomy did not result in eradication of the organisms. In view of these observations, the results obtained with penicillin in the elimination of the chronic diphtheria carrier state in 3 to 5 days appear very significant, and this type of treatment is worthy of further trial. The evidence obtained seems to indicate that a dosage schedule of 30,000 units of penicillin intramuscularly every 3 hours for 12 days is the most effective in the treatment of permanent diphtheria carriers.

The value of penicillin in the therapy of diphtheria appears to be its ability to shorten markedly the duration of the convalescent carrier state. There is no indication that penicillin has any beneficial effect on the clinical course of the disease, and its use does not eliminate the necessity of giving adequate quantities of antitoxin. The chronic diphtheria carrier state may be cured if adequate amounts of penicillin are administered parenterally.

Conclusions. 1. Penicillin has no effect on the clinical course of diphtheria, and its use in this disease does not eliminate the necessity of administering adequate amounts of antitoxin.

2. Penicillin reduces markedly the duration of both the convalescent and chronic diphtheria carrier states if given in sufficiently large quantities.

3. A dose of at least 120,000 and preferably 240,000 units of penicillin per day for 12 days is recommended for the treatment of acute diphtheria.

4. A minimum of 240,000 units of penicillin per day for 12 days is suggested for the treatment of the chronic diphtheria carrier state.

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THE EFFECTS OF BLOCKADE OF THE AUTONOMIC GANGLIA IN MAN WITH TETRAETHYLAMMONIUM

PRELIMINARY OBSERVATIONS ON ITS CLINICAL APPLICATION*†

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THE effects of tetraethylammonium, a quaternary ammonium ion, were essentially unnoticed until Acheson and Moe^{1,2} recently demonstrated in animals that it blocks transmission of nerve impulses through autonomic ganglia. It is the purpose of this report to describe the effects of such an autonomic blockade in man and to indicate the preliminary observations of its usefulness as a diagnostic and therapeutic agent in various disease states.

Pharmacology. Little information has been recorded in the literature concerning the action of the tetraethylammonium ion. It was noted³ that it was capable of preventing stimulation of ganglion cells by other quaternary ammonium compounds, and that it possesses a so-called "paralyzing nicotinic action."⁶ Acheson and Moe have studied the effects of the drug on the isolated dog heart¹ and on ganglionic transmission in dogs and cats,² using as test responses the reactions of the blood pressure, heart rate and nictitating membrane.

Tetraethylammonium bromide injected intravenously in doses of 0.1 to 10.00

mgm./Kg. causes a prompt fall of arterial pressure in animals. The depressor response is not the result of a direct action of the drug on the arteriolar smooth muscle since while intravenous doses cause an increase in the volume of blood flow through the femoral artery, intra-arterial injections of comparable doses cause no change. The blood pressure response is not due to a central action, but does not occur in the absence of vasoconstrictor tone. The drug causes no further fall of pressure after destruction of the medulla or section of the cervical cord. However, if vascular tone and blood pressure are restored by stimulation of the cervical cord distal to the point of transection, tetraethylammonium again causes a depressor response. If blood pressure is maintained by continuous infusion of epinephrine or angiotonin, tetraethylammonium causes no fall of pressure. Thus the drug does not prevent the direct effect of epinephrine, and the site of action must therefore be assumed to be in the sympathetic ganglia.

To prove that this action is in the gan-

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glia, the effects of the drug on transmission in the stellate ganglia were studied. Heart rate responses to ganglionic block would be expected to depend upon the existing balance between vagal and sympathetic tone. The drug causes no change in the rate of the denervated heart. When vagal tone is relatively high, as in animals under morphine-chloralose anesthesia, an increase of heart rate is the usual response to tetraethylammonium. Animals under dial or barbital anesthesia, in which sympathetic tone is high, respond with a decrease of heart rate. Section of the preganglionic stellate connections in such animals with a high sympathetic tone causes a decrease of heart rate; tetraethylammonium will now fail to cause a further change. If the heart rate is maintained at a high level by repetitive stimulation of the *preganglionic* fibers, the drug again causes cardiac slowing. If, on the other hand, heart rate is maintained by electrical stimulation of the *postganglionic* connections of the stellates, no change in heart rate follows injection of the drug. The site of action is therefore localized in the ganglia.

Similar experiments have been performed with the vagus nerves, except that stimulation of the postganglionic fibers in the mammal is not feasible. That the vagal blockade produced by the drug is ganglionic rather than terminal is suggested by the failure of the drug to diminish or block the cardiodecelerator or depressor effects of injected acetylcholine.

The ganglionic site of action has also been demonstrated in the superior cervical ganglion. If a sustained contraction of the nictitating membrane of the cat is induced by preganglionic stimulation of the cervical sympathetic nerve, tetraethylammonium causes relaxation of the membrane. The contraction induced by postganglionic stimulation is not affected by the drug.

Large doses of tetraethylammonium cause death of experimental animals, ap-

parently as a result of central respiratory paralysis. There is no curariform paralysis of muscles;³ death is in fact preceded by generalized muscle tremors, resulting from the direct action of the drug in high concentration on peripheral nerve or striated muscle. Local tremors are always apparent around an intramuscular injection site. The LD₅₀ of the bromide salt in mice is approximately 75 mg./Kg. intraperitoneally. Dogs have been killed by as little as 40 mg./Kg. intramuscularly.

EFFECTS IN MAN. *Methods of Administration:* Tetraethylammonium has been administered as the bromide or the chloride salt.* These salts are soluble in water and withstand autoclaving. They have been most satisfactory when administered in a 10% solution. A transient, but apparently maximal effect may be produced by the intravenous injection of as little as 0.1 gm. Larger doses may cause no greater effects, but the duration is more prolonged and the effects of the autonomic blockade become more apparent. In general 0.2 gm. to 0.5 gm. have been injected intravenously. The intramuscular dose should not exceed 20 mgm./Kg. body weight.⁹ Subcutaneous administration produces considerable discomfort at the site of the injection. This is also present to a minimal extent after the intramuscular injection, since some patients complain of a mild burning or tingling sensation followed by residual soreness at the site of injection. More discomfort is experienced with injections of higher concentration. Though the drug has been administered orally in doses of 4 to 6 gm., it produces very little physiological change even in patients who respond well to a parenteral injection. It is apparently poorly absorbed from the gastro-intestinal tract.

The Effects of Intravenous Injection: The intravenous injection produces a metallic taste in the mouth in 15 to 20 seconds. This is followed by a sensation of numbness and coldness of the hands and feet in about 25 to 35 seconds with

* Furnished by Parke Davis and Company, Detroit, Michigan, as Etamon, in 20 cc. sterile ampules through the courtesy of Dr. E. C. Vonder Heile.

subsequent paresthesia which quickly disappears. Shortly thereafter there is an incomplete dilatation of the pupil and a decrease in its reaction to light. There is some loss of accommodation. Ptosis of the upper eyelids occasionally develops. The patient feels "tired," "relaxed all over," "weak." Within 30 to 90 seconds there is a fall in both systolic and diastolic arterial pressures in the majority of patients with high arterial pressures and in some patients with normal blood pressure. (Fig. 1.) At the same time there is usually an elevation of the heart rate to between 90 and 120 beats per minute. Sweating, if present, stops. The mouth becomes dry. The temperature of the toes and fingers usually increases to that of the thigh or to about 33° C. The blood flow through the hands and feet as measured by the plethysmograph is increased. The systolic and diastolic pressures remain depressed for several minutes, then gradually increase to the initial level. Postural hypotension which develops immediately after the injection of the drug persists after the return of the blood pressure to its previous level and may last along with dilatation of the pupils and increased skin temperature for 15 to 60 minutes after a single injection. Vascular reflexes such as the effects of cold are abolished or greatly diminished at the height of the effects of the drug. At the same time there is cessation of propulsive gastro-intestinal motility so that barium in the gastro-intestinal tract may remain in the same position until the effects of the drug diminish. The bladder tone is diminished and the urge to void with bladder distention is lost. In spite of the fall in blood pressure there is a temporary increase in the cardiac output of about 20% as measured by the Starr type of ballistocardiograph in normal and in hypertensive subjects having essentially normal control ballistocardiographic waves. Normal subjects and patients with elevated venous pressures experience a significant decrease in venous pressure.

Effects of Intramuscular Administration: The intramuscular injection of 1-2 gm. will produce the same effects over a longer period of time. The arterial pressure may be depressed in hypertensive patients for 2 to 8 hours. (Fig. 2.) The skin temperature remains elevated and postural hypotension may persist over a longer period. The bladder atony becomes sufficiently pronounced so that the bladder may rise above the pubis, and the patient still has no desire to void. The gastro-intestinal tract remains quiet for several hours. During these effects, however, the patient is comfortable though there usually is weakness and faintness in the sitting position due to the postural hypotension.

Effect on Kidney Function: Though pronounced changes in the blood pressure may be experienced in patients with hypertension, there has been no evidence of impaired kidney function after the intramuscular injections. The urine volume is moderately reduced when there is a significant fall in arterial pressure. The renal blood flow has been measured in sixteen patients by the clearance of para-aminohippurate.¹² In normal subjects and in hypertensive subjects in whom moderate decreases in blood pressure were produced, clearance of para-aminohippurate* was not significantly changed. The glomerular filtration rate as measured by the clearance of sodium thiosulfate¹¹ was diminished in proportion to the fall in blood pressure.⁷ In animals with neurogenic hypertension, induced by elimination of the buffer nerves, the decrease in blood pressure resulting from administration of the drug was not associated with any change in renal blood flow as measured by a flowmeter or by the clearance of para-aminohippurate. It would appear likely therefore that tetraethylammonium must induce in some cases a moderate renal vasodilatation since the renal blood flow is maintained, as blood pressure falls. Vasodilatation is, however, apparently insufficient to maintain the renal circulation

* Sodium para-aminohippurate was generously supplied by Sharp and Dohme, Inc., Glenolden, Pa., through the courtesy of Dr. Karl Beyer.

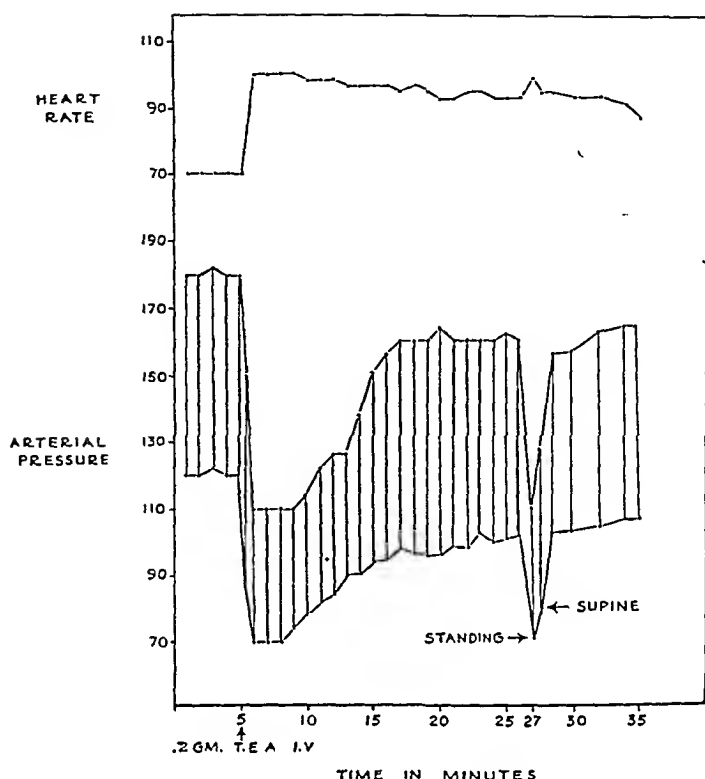


FIG. 1.—The intravenous administration of .2 gm. tetraethylammonium bromide produced a rise in heart rate from 70 to 95 beats per minute, with a fall in blood pressure from 175/116 to 110/70 mm. Hg. followed by a rapid return to the previous level with continued postural hypotension.

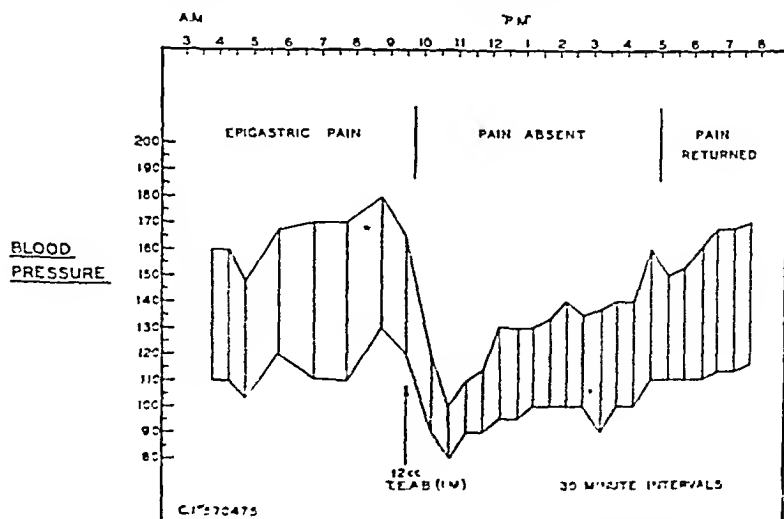


FIG. 2.—The intramuscular injection of 1.2 gms. of tetraethylammonium bromide in a hypertensive patient with duodenal ulcer. The patient had continued epigastric distress and hypertension while under hospital treatment with alkali and Meulengraecht diet for 5 days before the test. The pain was completely relieved for the first time in many weeks. The test was repeated the next day with similar results.

during the sudden and profound reduction in blood pressure occasionally noticed after the intravenous administration of the drug in patients with very severe hypertension. Under these circumstances there has been a pronounced decrease in the renal blood flow and also a decrease in the formation of urine. This might be expected in patients with malignant hypertension where the organic renal arteriolar changes may be irreversible. It might also be explained as a result of peripheral circulatory failure which was suggested on some occasions.

Excretion of Tetraethylammonium: Tetraethylammonium appears to be almost quantitatively excreted in the urine. It can be recovered from urine by precipitation with Reinecke salt as in the determination of choline.⁸ About 50% of the intravenous dose can be recovered in 30 minutes, while in 3 hours 50% of the intramuscular dose appears in the urine in the normal subject. Nearly all can be recovered in 24 hours. With oral administration only 6 to 15% can be found in the urine in 24 hours, suggesting that it is poorly absorbed from the gastro-intestinal tract.

Clinical Effects. It would seem from the above observations that the changes noted after the administration of tetraethylammonium are best explained by a blockade of both the parasympathetic and sympathetic nervous systems. The finding in animals of an increase in femoral arterial blood flow even in the presence of a fall in blood pressure, and the rise in peripheral skin temperature and blood flow in human subjects suggest obliteration of vasoconstrictor tone.

Peripheral Vascular Disease: The most striking clinical application has been in patients with arterial insufficiency of the extremities associated with vasospasm. The administration of tetraethylammonium has relieved this vasospasm so that even though there is a fall in blood pressure the skin temperature has increased to the same degree as that found after spinal anesthesia or after lumbar sympathectomy. (Fig. 3.) This has also been associated

with dramatic relief of rest pain or intermittent claudication in a few cases. The vasoconstriction once relieved has, in some cases, failed to return. This has been especially striking in patients with Buerger's disease who have had continued relief of pain and a decrease in the inflammatory process following injections of the drug. In a few cases with obliterative vascular disease, pain has been relieved even though there was no change in skin temperature. The ability of tetraethylammonium to relieve vasospasm has made it a useful diagnostic tool in evaluating the role of neurogenic vasoconstriction in patients with arterial insufficiency who may be selected for lumbar sympathectomy. It has proven to be as reliable as paravertebral block or local nerve block.

Patients with thrombophlebitis and vasospasm have responded well with increase in skin temperature and, after repeated injections, a disappearance of the inflammatory process and edema. More details concerning its use in peripheral vascular disease has been presented.⁴

Causalgia: The drug has also been of value in relieving pain in many different types of causalgia and in post herpes zoster neuralgia. In a few instances the pain has been permanently abolished. In other cases pain has been relieved during the action of the drug and has been less severe as the effects of the drug disappeared. It has served as a useful diagnostic tool in the selection of cases of causalgia which might be relieved by sympathectomy.

Hypertension: The production of blockade of the autonomic ganglia is associated with a decrease in blood pressure, especially in hypertension. In normal subjects with initially low diastolic pressures there is little change in the blood pressure. In 143 hypertensive patients there was an average fall in diastolic pressure of 193 mm. and in systolic pressure of 23.5 mm. following injection of the drug. In spite of such a fall in blood pressure there has been relatively little change in the appearance of the retinal vessels.

It may be significant that 26 patients

with hypertension failed to have a fall in blood pressure with a test dose of the drug. In the majority of instances we have been unable to determine why these subjects failed to have the usual depressor response. A few of these subjects had uremia. Two had only one kidney, but most had the clinical diagnosis of essential hypertension. In some it is possible that epinephrine liberated as a result of apprehension over the injection and the frequent

ities. The older hypertensive patients seem to have a somewhat greater depressor response.

In some patients with malignant hypertension or with very severe essential hypertension there has been a profound fall in blood pressure followed by circulatory collapse. The collapse is accompanied by extreme weakness, drowsiness, yawning, and is associated with slowing of the heart, the development of nausea and, at times,

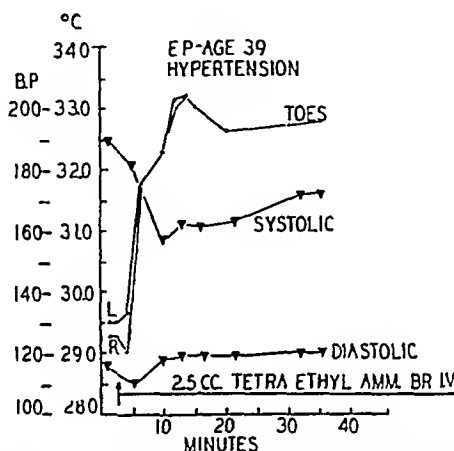


FIG. 3—The effect of 0.25 gm. of tetraethylammonium bromide on the toe temperature of a hypertensive patient whose skin temperature had been constant in a room of 68° F. The patient had no evidence of peripheral vascular disease.

blood pressure determinations may have been sufficient to prevent the action of the drug. It has been noted that tetraethylammonium fails to overcome the pressor action of epinephrine. In a few cases repeated tests with an intramuscular injection were followed by a depressor effect when none had been noted with the initial intravenous administration of the drug.

In some patients with nephritis or in patients with essential hypertension and impaired kidney function the response to the drug was similar to that found in uncomplicated essential hypertension. A similar response has also been noted in toxemia of pregnancy. In one case of coarctation of the aorta there was not only a significant decrease in both systolic and diastolic pressure, but also a pronounced increase in skin temperature of the extrem-

ities. In some cases there was vomiting or temporary loss of consciousness and profuse perspiration even though the blood pressure may have fallen only to 150/90. Under these circumstances there is a drastic reduction in renal blood flow. Most of the patients recover spontaneously from this state within a few minutes. In some the subcutaneous administration of epinephrine has promptly restored the circulation.

In a few hypertensive patients with severe nuchal headaches associated with an elevation of pressure above the usual level and with vertigo, nausea, vomiting, or recent impairment of vision, the administration of tetraethylammonium has been helpful in relieving these symptoms as well as in decreasing the blood pressure. In such cases and in some without symptoms the blood pressure failed to return to its

previous level after the administration of the drug. The decrease in blood pressure in these patients was of the same degree as that usually found after several days of hospital rest.

In a few patients with dyspnea and orthopnea associated with hypertensive heart disease and heart failure, the use of the drug was followed by a decrease in the severity of the symptoms. One patient with severe orthopnea, in spite of continued hospital treatment, was completely relieved for as long as twelve hours. Patients with nephritis and uremia as well as orthopnea were not relieved of their symptoms.

The decrease in blood pressure noted after such an autonomic blockade might suggest that it would be useful in the selection of hypertensive cases for sympathectomy. The blood pressure response to intravenous or intramuscular administration of tetraethylammonium has been recorded preoperatively in 51 patients subjected to supradiaphragmatic splanchnicectomy. At present an insufficient time has elapsed for the evaluation of the postoperative results. The blood pressure two weeks after the operation was somewhat similar to that found during the administration of the drug. In 13 cases the diastolic pressure failed to fall below 110 with the drug and in 11 of these cases it continued to be above 110 after the operation. In 38 cases the blood pressure fell to 110 or below with the drug and was found to be 110 or below in 28 cases two weeks after operation. In general there was a greater fall in blood pressure with the drug than that experienced two weeks after supradiaphragmatic splanchnicectomy. But a linear correlation of this relationship has been unsatisfactory up to the present time. This is to be expected, of course, since the sympathetic control of the extremities is not altered by this type of operation. The diastolic pressure two weeks after the operation represents, in general, the maximal effect of the procedure in lowering the blood pressure. An average increase in diastolic

pressure in the next year of about 15 mm. of mercury can be expected.

Attempts have been made to maintain the blood pressure at a lower level by continuing the autonomic blockade with repeated intramuscular injections. This has caused moderate discomfort to the patient. When the drug was discontinued the blood pressure returned to its previous level.

Coronary Artery Disease: The possibility of the development of coronary ischemia and angina pectoris as a result of the sudden decrease in blood pressure in hypertensive patients was considered, but it has not been observed. In fact, the intravenous administration of the drug in 2 cases has dramatically relieved the pain of acute myocardial infarction in the presence of a significant fall in the blood pressure without the development of further changes in the electrocardiogram. Similar observations have been made in a few patients with angina pectoris at rest in whom no pain or change in the electrocardiogram developed with transient decreases in the blood pressure in one case from 170/110 to 60/40.

Though tetraethylammonium has relieved the pain of acute coronary thrombosis or angina pectoris, we do not have sufficient information at present to explain this action. It would not seem advisable to use it for this purpose until more details are available concerning its action on the coronary arteries in the presence of a fall in arterial pressure.

Gastro-Intestinal Tract: The cessation of gastro-intestinal motility observed fluoroscopically with the barium meal is also apparent clinically. In patients with pain resulting from a peptic ulcer the administration of the drug is followed by immediate relief of the pain and by a decrease in peristaltic sounds. (Fig. 2.) As the effects of the drug wear off pain returns and peristalsis may even be more rapid. In a similar manner abdominal cramps and diarrhea may be temporarily abolished by the administration of tetraethylammonium. It not only produces a cessation of gastro-

intestinal motility but also has significantly decreased the acidity and the volume of gastric juice in an unstimulated stomach. However, it does not alter the effect of histamine on gastric secretion.

Though it has favorably altered headaches in hypertensive patients, no effect has been noted in a few so-called migraine headaches. It has no analgesic effects on the usual types of somatic pain. A trial of the drug in eight patients with dysmenorrhea has not been successful in relieving the pain which suggests that the mechanism of pain is different from the muscle cramps of the gastro-intestinal tract.

Toxic Effects. Though the drug has been administered over 1000 times to more than 400 cases, very few serious effects have been noted. In a few hypertensive patients and those with generalized arteriosclerosis, there has been a severe fall in blood pressure associated with other evidence of peripheral circulatory collapse. The drug should be used cautiously in severe hypertension particularly when renal function is poor. In 4 subjects the extravascular injection of the drug in the antecubital fossa was associated with a flexor spasm which persisted for only a few hours and was apparently the result of local action of the drug on the nerve trunks. Four female subjects who received large doses of the drug developed a sudden onset of hyperventilation similar in many respects to hysterical hyperventilation with a further rise in pulse rate and blood pressure. They complained of difficulty with inspirations, possibly related to retention and drying of the bronchial secretion. This quickly subsided with no ill effects. In general, intravenous or intramuscular injections produce little change in respiratory excursions. Some have had an increase in respiratory rate for a few moments immediately after the intravenous injections. Respirations, of course, become very slow in those patients who developed peripheral circulatory collapse.

Some patients complained of dysphagia which was associated with profound dry-

ness of the mouth, making it difficult to swallow.

In a few patients, the sensation of weakness and fatigue and light headedness was very pronounced; they appeared to experience difficulty with muscle movement though when tested there was no loss of strength or change in the muscle reflexes. The sensation is associated with dulling of the sensorium so that integration of movement is somewhat more difficult; speech is slowed but not impaired except by the very dry mouth. The patients have trouble explaining the sensation. This was experienced more often after repeated injections at short intervals or after large doses and occurred at times without a fall in blood pressure. The explanation of this apparent weakness is not clear, but it seems likely that it is of central origin. In animals depressor doses of the drug may increase the muscular response to electrical stimulation of the nerve; curariform action on muscles has been noted only after very large intra-arterial injections of the drug.³ In some small patients who have received rapid intravenous injections of 0.5 gm. or more and in obese patients given large intramuscular injections, muscle tremors have been noted a few minutes after the injection. These are irregular in character, and usually quite transient. The patients describe it as a rigor similar to a chill though they are not cold.

Repeated intramuscular injections with resulting continued autonomic blockade produces a variety of complaints. The inability to void or to defecate at times alarms the patients. The loss of accommodation limits the patients' ability to read. The dry mouth is annoying. Many patients have a loss of appetite and in some a sensation of nausea. The postural hypotension is sufficiently severe so that the patient must remain supine. Some who have attempted to stand have, of course, felt very faint or have collapsed. In general continuation of the autonomic blockade longer than 36 hours has caused considerable distress to the patient.

Conclusions. 1. Tetraethylammonium administered to man in doses of 0.2 to 0.5 gm. intravenously or up to 20 mg./Kg. intramuscularly produces a series of changes which are best explained by blockade of the autonomic ganglia.

2. The effects on the cardiovascular system are primarily the result of the release of vasoconstrictor tone; there is an increase in skin temperature, a transient fall in both systolic and diastolic pressure, postural hypotension, a fall in peripheral venous pressure and an increase in heart rate and cardiac output. These effects have been applied clinically in peripheral vasoconstrictive states, in relief of pain due to ischemia, in the relief of vasospasm, and as a diagnostic procedure.

3. It produces a cessation of normal peristalsis in the gastro-intestinal tract and a diminution in gastric secretion. This has been applied clinically for the relief of pain and increased motility of the gastro-intestinal tract. There is also a decrease in salivary secretion, cessation of sweating, incomplete dilatation of the

pupil with loss of accommodation. The tone of the urinary bladder decreases and the urge to void is abolished.

4. There has been significant relief of pain in causalgic states, which in a few instances failed to return after the immediate effects of the drug had disappeared.

5. Toxic effects have been chiefly due to the ganglionic blocking action of the drug.

6. Tetraethylammonium is a useful tool for the further study of disorders affecting the autonomic system.

7. It is helpful in the selection of patients in whom surgery on the autonomic nervous system is to be considered.

8. In selected cases the use of the drug may be of therapeutic as well as diagnostic value, especially in peripheral vascular and causalgic states.

9. Though it will produce a transient fall in arterial pressure and has relieved symptoms of the complications of hypertension in a few instances, treatment of hypertension by repeated use of the drug does not appear feasible.

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INSENSITIVITY TO EPINEPHRINE IN A PATIENT WITH A FUNCTIONING TUMOR OF THE ADRENAL MEDULLA

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THE syndrome associated with tumors of the adult chromaffin cells of the adrenal medulla is well-known and excellent summaries^{2,9,11} of the literature on this condition are available. However, the data pertaining to the important matter of loss of sensitivity to epinephrine in such cases are extremely meager. The effects of small doses (0.5-1.25 cc.) of 1:1000 epinephrine have been studied by other investigators.^{4,7,10,11,12,13,14} No attacks followed, and few other data were reported. In none of these instances were the doses of epinephrine increased to the maximal level employed in the case we wish to report. We administered increasing doses of epinephrine both while the tumor was present and after its removal. Our results showed that the patient was definitely hyposensitive to epinephrine action while the tumor was present; this hyposensitivity disappeared after its extirpation. We also studied the patient's response to the administration of acetyl- β -methyl choline, and amyl nitrite, took electrocardiograms and ballistocardiograms before, during, and after attacks; determined changes in many of the chemical constituents of the blood; assayed the epinephrine content of the tumor; measured the urinary epinephrine; determined the amount of choline esterase in the blood, and measured muscle potassium content.

Case Report. J. G. was a 42-year-old white male who was well until 2½ years before admission to the Hospital, at which time he began to have attacks of palpitation (a slow, hard heart beat) headache, pain in the epigastrium, perspiration, lacrimation, and salivation. Each attack lasted from

30 minutes to 2 hours and while they occurred irregularly at first, about one year before admission the frequency increased until they were occurring from 1 to 16 times a day. In the more severe attacks, nausea and vomiting with back pain were present, and when the attacks were wearing off a feeling of swelling in the neck was frequently experienced with actual increase in neck size due to venous engorgement. These episodes were often brought on by physical exercise or changes in position such as lying down.

On physical examination there were no abnormalities save a few pigmented naevi from 2 to 5 mm. in diameter which were scattered over his trunk. His blood pressure on first examination was 130/80; blood pressure changes during a typical attack may be seen in Figure 1.

Numerous attacks were witnessed during his hospital stay. The initial phenomenon was a slow, forceful, and often irregular beat seen over all of the major superficial arteries. The extremities were then noted to be blanched and cold, and the patient began to perspire slightly. Distention of the small and deep veins of the neck became increasingly prominent as the attack progressed, while venipuncture of the forearm veins became difficult due to spasm. In the more severe attacks epigastric pain developed with nausea and vomiting. Salivation and lacrimation were seen early but soon disappeared. After the first phase of cardiac slowing to about 60 beats per minute the heart rate increased. No changes in the measurements of the pupils occurred. Swelling of the neck was obvious long after all other signs had disappeared.

Routine studies were as follows: a complete blood count, urinalysis, Kolmer and Kline reaction, and chest film, all with no abnormalities. The basal metabolic rate was +8 per cent. The values for the 100-gm

5-hour glucose tolerance test were: fasting 75, 1 hour 224, 2 hours 73, 3 hours 54, 4 hours 63, 5 hours 83 mgm/100 ml. Blood sugar values during an attack showed no striking rise (see Figure 1).

The intravenous urogram was reported as showing a slight lateral and downward displacement of the superior pole of the right kidney. In some of the films a vague, rounded mass could be seen medially and superior to the right kidney. Perirenal air insufflation was not attempted because of its potential dangers.

On September 13, 1945, the patient was operated upon by Dr. Jonathan Rhoads of the Surgical Service of the University Hospital through a right rectus incision under endotracheal cyclopropane anesthesia. The approach through the right side was chosen because of the suggestive findings in the urogram. A tumor of about the size of a tennis ball was found in the region of the right adrenal, while palpation of the left adrenal area revealed nothing abnormal. The tumor was quite adherent to adjacent structures and during the operation the capsule was torn, necessitating piecemeal removal. At one point during the operation the blood pressure rose to 320/160 and the pulse to 180, but on the whole the patient withstood the operation quite well. The blood pressure was well maintained after operation and, while no evidence of adrenal cortical failure developed, desoxycorticosterone was given prophylactically. Convalescence was uneventful. On examination five months later no complications or evidence of recurrence had developed.

Pathological report by Dr. R. C. Horn was as follows: "The tumor is highly cellular, having little stroma, composed almost entirely of delicate, but often large, capillaries. The tumor cells uniformly are large and more or less rectangular. The nuclei vary moderately in size but are usually ovoid and vesicular with a small nucleolus. The cells are arranged in clusters or in undulating cords with their long sides parallel. They show a striking tendency to be arranged perpendicularly, along or about blood vessels. The cytoplasm is usually stippled with fine granules which are blue in hematoxylin and eosin stains and brownish red in Trichrome prep-

arations. There is considerable hemorrhage but in general the tumor is well preserved. The morphology is that of endocrine gland tumors in general and coincides with the usual pheochromocytoma or adrenal paraganglioma. Most of these tumors are benign and it is likely that this one is also. However, occasional bizarre, gigantic tumor cells and mitotic figures are present and tumor cells are seen in a few blood vessels. This latter finding may be without significance. Nevertheless, malignancy must be considered as a possibility, although unlikely. The skin lesion is a mole showing little pigmentation."

The total weight of the tumor was 42.8 gm. Except for the small samples taken for pathological studies, the pieces of tumor were immediately frozen in dry ice and sent to Dr. Carl Beyer of the Sharp and Dohme Laboratories and assayed for epinephrine content. The tumor contained 76.5 mg. of free epinephrine by the colorimetric method of Beyer and Shapiro.¹ No conjugated epinephrine was found.

At the time of operation a small piece of rectus muscle was removed and later analyzed for potassium content. This was found to be 172.0 m.Eq/Kgm. of wet muscle. According to Fenn's⁶ review of the literature, the normal values for muscle potassium found in humans by Katz and others was 82 m.Eq/Kgm. of wet muscle.

STUDIES OF THE ATTACKS. As part of our study, an attempt was made to discover what stimuli were effective in producing an attack. The patient stated that emotion was not a factor. Injections of sterile water given before each testing were found to be ineffectual. Exercise or postural changes such as lying down usually produced attacks as described previously. Typical attacks were easily produced by having the patient bend and twist his waist or by pressing his knees into his abdomen. Manual massage of the adrenal area proved ineffectual.

The patient was given 10 mg. of acetyl- β -methyl choline subcutaneously to deter-

nine whether this drug would cause functional stimulation of the tumor. The effect of the administration of this drug was very dramatic, for, in addition to the usual acetyl-choline like effects, the patient had one of his most severe attacks. Atropine was not given to counteract the acetyl-choline effects, for it was feared that abolishing the depressant effects of the vagus on the heart might cause a disastrous increment of blood pressure. It was

amount was increased to 1.0 cc. and 1.5 cc. with no detectable result except the usual pilomotor response at the site of injection. When 2.0 cc. were given, a slight rise in blood pressure occurred (to 162/98) but no symptoms were experienced. However, 2.5 cc. gave a blood pressure rise to 220/114 and the patient noted the symptoms that usually occurred with a mild attack.

The inhalation of a pearl of amyl nitrite

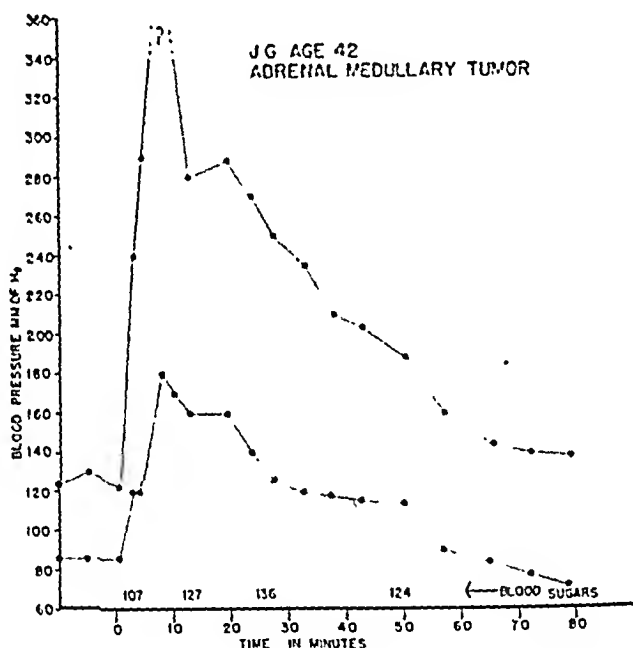


FIG. 1.—Variations in blood pressure and blood sugar concentration during an attack induced by exercise.

not deemed advisable to repeat the injection of acetyl- β -methyl choline because of the severity of the reaction.

The effects of epinephrine were next studied (Figure 2). The solution used was first compared with the U. S. P. standard epinephrine by Dr. H. D. Bruner of the Department of Pharmacology, and found to be of standard strength. The same solution was used throughout all tests.

When 0.5 cc. of 1:1000 epinephrine was given subcutaneously, no discernible effect on the patient or change in his blood pressure was noted even after vigorous massage of the site of injection. The

was next tried in order to determine whether the resulting fall in blood pressure common to this compound and acetyl- β -methyl choline was a factor in producing an attack. Flushing, headache, and a fall in blood pressure of 40 mm. of mercury resulted, but no attack occurred.

Electrocardiograms were taken before, and 4, and 15 minutes after the onset of an attack. The standard limb leads were taken and in addition CR2, CR3, CR4, and CR5 leads. When no attack was present, the most striking changes were inversions of T-waves in I, II, and CR5, with low or flat T-waves in III, CR2 and

CR4. Four minutes after the onset of an attack, A-V nodal rhythm was present with a rate of 65 and the previously low or inverted T-waves were now elevated to normal or slightly above normal heights. Fifteen minutes after the onset of the attack the electrocardiograms had returned to the same form they showed before the attack.

Ballistocardiograms¹⁶ were taken when no attack was present and at repeated intervals after an attack had been induced. The form of the records was normal when no attack was present, but the cardiac output was 52% above average normal. Four minutes after the onset of an attack, the form of the record was completely confused, and the amplitude relatively small. As recovery took place, the record gradually returned toward normal, but the form was now of the "late down-stroke type." This abnormality is characterized by a small I wave, often notched, and a prominent K-wave; these abnormal forms are frequently seen in patients with severe circulatory abnormalities. The results of additional studies are summarized in Table 1.

POSTOPERATIVE STUDIES. Manipulation which had caused attacks before operation failed to do so after it. Ten mg. acetyl- β -methyl choline produced its usual response but no attack ensued. A most striking change was noted in the patient's reaction to epinephrine (Figure 2). After the injection of 0.25 cc. of 1:1000 epinephrine subcutaneously, a definite rise in blood pressure to 172/98 occurred with all of the previous symptoms of a typical attack. This time, however, he complained of nervousness which he had never experienced before even during his worst episodes. When the amount of epinephrine was increased to 0.5 cc. and 1.0 cc., a correspondingly greater rise of blood pressure and more severe symptoms occurred.

One month after operation the electrocardiograms were almost entirely normal, the only persisting deviation being a slight flattening of the T-waves in the limb leads. After the injection of 0.25 cc. of 1:1000 epinephrine subcutaneously, a tachycardia occurred with the development of flattening of the T-waves in all leads.

The ballistocardiogram one month after

TABLE 1.—RESULTS OF VARIOUS ANALYSES IN AND OUT OF ATTACKS

	Normal Range	No Attack Present	23 Minutes after Onset of Severe Attack
Serum Calcium mg./100 ml. . . .	9-11	9.5	..
Serum Magnesium m.Eq/100 ml. . .	1.8-2.2	1.9	.
Serum Cholesterol mg./100 ml. . . .	150-190	291	...
Serum CO ₂ vol./100 ml.	50-71	61	50
Serum Chloride m.Eq/100 ml. . . .	98.5-104.5	99.8	100
Serum Protein gm./100 ml.	5.9-7.0	5.6	5.9
Serum Total Base m.Eq/100 ml. . .	142-149	153.8
Serum Potassium m.Eq/100 ml. . .	3.8-4.3	5.0	2.9
Serum Urea Nitrogen mg./100 ml. .	22-29	20	.
Serum Volume ml. (T 1824)	2000±	2400	.
Extracellular Fluid Per cent Body Weight (Thiocyanate)	20-28	27.3	.
Water Excretion Test, A Value (Robinson, Power, Kepler) . . .	25+	4	.
Urinary 17 keto steroids mg./24 hour (Zimmerman)	12-19	6.1	...
Urinary Conjugated Epinephrine mg./100 cc.	0	0	0.45*
Plasma Choline Esterase† (micro mols of CO ₂ /30 min.)	10-18	13	.
Red Cell Choline Esterase† (micro mols of CO ₂ /30 min.)	9-13	10.2	.

* In 163 cc. urine collected during attack.

† Bodansky's modification of Ammon's method.

operation was normal in form, but the cardiac output had increased to +86%. Five months after operation, the cardiac output was still +43%. At this time the response of his circulation to 0.5 cc. of epinephrine given subcutaneously was the usual one seen, an increase in cardiac output of 40% above the base line value.

Comment. Although emotion did not produce attacks in our patient, other

producing an attack is uncertain. The events may have been coincidental or they may have been secondary to massage of the gland by diaphragmatic action or changes in intra-abdominal tension. Kvale and Roth⁵ found 2 mg. of acetyl- β -methyl choline ineffective in producing an attack in their patient, but did produce repeated attacks in 3 patients by the use of intravenous histamine.

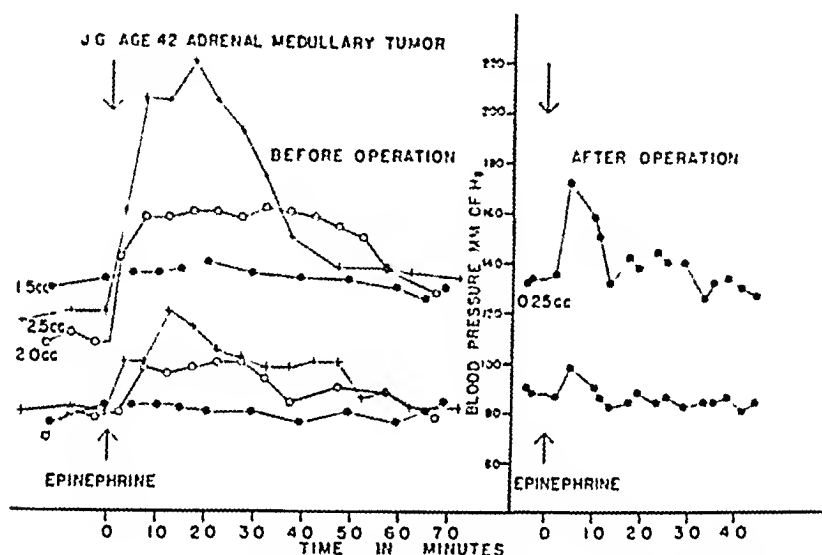


FIG. 2.—Effect of varying doses of epinephrine on blood pressure (a) before and (b) 5 months after removal of pheochromocytoma.

observers¹⁸ have reported that emotion did serve as an inciting factor. Since a lack of physiological rapport with the rest of the body is one of the characteristics of all tumors, one wonders whether the attacks reported after emotional upset were due primarily to nervous stimulation of the tumor, or were instead secondary to pressure on the tumor. These tumors are usually directly under the diaphragm where they would tend to be compressed by the sudden deep inspirations of the changes in intra-abdominal tension consequent to excitement. Postural changes undoubtedly work through this same mechanism.

The reason for the effectiveness of the 10-mg. dose of acetyl- β -methyl choline in

The postoperative increase in sensitivity to epinephrine in our patient was quite striking (Figure 2). As may be seen by the graph, 0.25 cc. of epinephrine given after operation produced a higher blood pressure rise than did 2.0 cc. before operation. It should be noted, however, that the rise in blood pressure was more sustained with the larger amount.

Although some pharmacologists^{5,15} do not believe that tolerance is developed to epinephrine, it is a well-known clinical fact that "fastness" to epinephrine occurs in asthmatics receiving large doses over a long period of time. The development of tolerance to epinephrine could perhaps be more reasonably anticipated in patients with functioning tumors of the adrenal medulla than in any other group, especially

if the tumor had been active for a long time. Strombeck and Hedberg,¹⁷ using a colorimetric method, reported that the blood epinephrine levels were 30 times normal in a patient with pheochromocytoma when no attack was present and the blood pressure was normal. Beer *et al.*,¹⁹ using a rabbit ear perfusion, claimed evidence of increased vasoconstrictor action in blood drawn from his patient during an attack. These observations, together with the rapid fall in blood pressure which often occurs immediately after the removal of such tumors or even after interruption of their venous circulation, suggest that the normal pressor mechanism may undergo some type of compensatory adjustment to the constant or intermittent presence of large amounts of epinephrine in the blood stream.

The phenomenon of epinephrine resistance, if constant, should be of use clinically and might constitute a relatively harmless test for functioning adrenal medullary tumors. Since these tumors are so rare, it is impossible for any one group of investigators to collect more than a few cases, so experience must be built up slowly.

The electrocardiographic changes described by us have been reported by other observers^{3, 8, 12} in cases of pheochromocytoma. The A-V nodal rhythm is best explained as a vagal phenomenon since other evidences of a parasympathetic discharge in the form of salivation, lacrimation, and perspiration were present. Elevation of the T-waves during the attack is, as far as we know, unexplained, and is the reverse of what might be expected to result from the fall in serum potassium concentration observed during an attack. The depression of the T-waves by epinephrine after operation in spite of a blood pressure rise suggests that the phenomenon is not due to the epinephrine

alone, but some other factor must be present.

The ballistocardiographic abnormalities which developed during attacks were those which might have been expected with a heart working under heavy strain. After operation, the patient's temporary increase in cardiac output from +52% to +85% suggests an over-compensation of the heart after recovery from the strain of maintaining the repeated bouts of hypertension. Five months after operation, the cardiac output was once more near the preoperative level, +43%.

In our chemical analyses, we were able to confirm the findings of MacKeith,¹¹ that the serum potassium was elevated. This was only true when no attack was present, the value being significantly below normal during an attack. Another feature was the increase in muscle potassium to over twice the values given in the literature. These evidences of disturbances in potassium metabolism are quite striking and should be investigated in other cases. The serum changes may be of aid in recognizing the disease. The significance of these changes is still uncertain, but they suggest the possibility of intermittent variations in adrenal cortical function. This possibility is further supported by the decrease in urinary 17-keto-steroid excretion and the low A value in the water excretion test, although the patient did not present symptoms suggesting adrenal cortical failure.

Summary. 1. Insensitivity to epinephrine was demonstrated in a patient with a functioning tumor of the adrenal medulla.

2. A return of normal sensitivity to epinephrine followed surgical removal of the tumor.

3. The suggestion is made that the demonstration of such insensitivity may serve as a useful and harmless test for the diagnosis of such tumors.

We are indebted to Dr. Joseph Aspel for the opportunity of studying our patient. We wish to thank Dr. Carl Reyer, Dr. F. W. Sunderman, Dr. Julius Comroe, and Dr. H. D. Bruner for valuable contributions to our data. Dr. Isaac Starr contributed suggestions and reviewed the ballistocardiograms. Our electrocardiograms were reviewed by Dr. C. C. Wollerth.

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INCREASED REACTIVITY CAUSED BY ADRENALIN

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THE action of prolonged administration of adrenalin in reducing the reactivity to the drug has already been reported (Cameron^{2c}).

We have now observed instances in which the administration of adrenalin may have the reverse effect, namely, it may increase the reactivity of the individual to the drug. This communication consists in a report of such instances and an attempt to evaluate the light which they throw upon the development of the chronic tensional anxiety states. The phenomena observed fall into 3 groups: (a) Head and neck aches, (b) Increased cardiovascular activity, and (c) Venous phenomena.

Head and Neck Aches. Very severe headaches were noted in patients who were receiving intravenous and intramuscular adrenalin therapeutically. These patients were suffering from various degrees of tensional anxiety state and were being treated with injections of adrenalin which varied from .001 mg. to .09 mg. intravenously and from .4 mg. to 2.0 mg. intramuscularly (Cameron^{2c}). Out of 42 patients receiving these injections over periods which ranged from 3 months to 2 years, 7 developed severe headaches: 3 patients had headaches on one occasion only, 2 patients experienced these headaches on 2 occasions, 1 on 6 occasions and 1 on numerous occasions over a period of 43 days.

Location. An outstanding feature of these headaches was their location. Without exception they involved the occiput and the back of the neck, extending, in several instances, in the form of an aching sensation as far down as the first dorsal vertebra. In 2 patients other areas were involved as well. One patient stated that the headache commenced in the frontal region, then was experienced primarily in the right side, but within one-half hour

was complained of principally in the occiput and neck areas. One patient complained of aching in the left temporal region, as well as the occiput and neck.

Preliminary comment may be made of the occurrence of aching of the neck and occipital headaches in patients suffering from tensional anxiety states (Wolff,⁸ Cameron^{2b}).

Description. The headaches were invariably sudden in their onset, reaching full intensity within $\frac{1}{2}$ to 1 minute after intravenous injection and within 4 to 5 minutes after intramuscular injection. In all cases the headache was primarily throbbing in nature; in 1 case it started as an ache but became throbbing within 20 minutes. The intensity was considerable, the patients looking alarmed and remaining motionless. In most instances there was an extension to the neck in the form of an aching stiffness and some pain on movement.

As to duration, apart from one mild headache which disappeared in 50 seconds, all the others lasted for periods ranging from 30 minutes to 8 days. The longer headaches persisted primarily in the form of an aching of the neck.

Relation to Cardiovascular Reactivity. The relation of these headaches to the reactivity of the cardiovascular system is important. The headaches most commonly appeared when the systolic pressure rose above 170 mg. Hg. and still more commonly when the difference between the pre-injection and post-injection pressures was more than 50 mg. Hg. (Table 1). The relative, rather than the absolute, rise seems to be the more important, since rises to 250 mg. Hg. have been elicited, without the production of headache, in hypertensive patients whose basic systolic blood pressures were over 200. It was noted, moreover, that the headaches were

more apt to appear when the blood pressure rise to a given dose had been greater than on previous occasions. Since, however, the blood pressure recording was not completed until the 90th second after injection and the headache had already set in by this time, it is not clear whether this greater response to the injection actually represented a greater reactivity or whether it was due to the anxiety produced by the headache. The reactivity of the pulse tends to be limited by the blood pressure rise and the most common immediate response was a slight brachycardia.

ance of the symptoms, but as the patient was not usually content simply to wait, more active measures were sought. It was found that a histamine hydrochloride solution, containing 0.1 mg. of the drug, given intravenously over a period of 6 minutes caused a disappearance of all complaints during the period when the patient was flushing in response to the histamine. These effects, however, were not permanent and after the histamine had been discontinued, the throbbing and aching tended to return in their former intensity. It was finally discovered that the most effective measures were deep massage of

TABLE 1.—APPEARANCE OF HEADACHE IN RESPONSE TO INTRAVENOUS INJECTION OF ADRENALIN

Miss N. S.		March 25, 1945			
	Time	B. P.	Pulse	Remarks	
Initial Recording .	2 P. M.	116/76	72	Feels well save for a cold. Has had no anxiety attacks even though she missed a treatment during the week.	
1st injection					
1 min.	2:15	140/72	72		
10 min.		114/74	63		
Amount 0.04 mg.					
2nd injection					
1 min.	2:25	196/106	72	HEADACHE—in back of neck. Began in less than 2 mins. after injection. Not a throbbing headache—located posterior to left sternocleidomastoid. Seems to disappear with massage of area.	
10 min.		128/80	64		
Amount 0.07 mg.					
3rd injection					
1 min.	2:40	160/96	63	Throbbing in same area after third injection. Aching. 25 mg. papaverine hydrochloride intravenously.	
10 min.	2:43	130/90	78		
Amount 0.04 mg.					
4th injection					
Not given	3:12	114/88	69	Neck not aching—but sore. Otherwise feels fine.	

Note:—(i) Large rise in B. P., with headache, in response to second injection.

(ii) After headache appears, response to 0.01 mg. adrenalin hydrochloride is substantially greater than before headache. (Compare 1st and 3rd injections).

Alleviation. A number of agents were employed in an attempt to alleviate the head and neck aching, and in the anticipation that they might throw further light upon the mechanism involved. Sodium nitrite (gr. 1 to 3) by mouth and papaverine hydrochloride (mg. 16 to 64) intravenously were found to be of little value. Aspirin, and intravenous sodium amyral, gr. $7\frac{1}{2}$, were found to reduce the patient's complaints, but there was no indication that this was due to control of the factors directly producing the aching.

As implied earlier, rest, for several days if necessary, resulted in a gradual disappear-

the muscles in the occipital area and along the back of the neck, together with the application of radiant heat. Under these circumstances, relief of the head and neck aches appeared rapidly and was considerably more lasting than that following the use of the other agents.

Increased Cardiovascular Activity. Of special significance is the subsequent reactivity of the cardiovascular system. In all instances it was found that the reactivity of the blood pressure and the pulse to adrenalin was considerably increased and often increased over a period of several days. This is in marked contrast to the

fact that repeated administration of adrenalin over extended periods tends to reduce the reactivity of the pulse and blood pressure to adrenalin (Cameron^{2c}).

It was found in addition, that once headache had been produced it was almost impossible to give the same dose of adrenalin on a subsequent occasion during that day without eliciting another attack of headache. Indeed, in most patients, as long as 3 days after the headache had first appeared it was necessary to use a dose of adrenalin reduced by 50%. Before this had been recognized, our attempts to continue treatment at the same dose level perpetuated attacks of headache in one patient over a period of 43 days. Ultimately, in this case, it was necessary to reduce the dose to one-fifth of the original.

The observation was also made that, in almost every instance, for several days after the headache had been elicited the reduced dose of adrenalin would produce a considerably greater blood pressure rise than it had on earlier occasions. It was also observed that, in the majority of the patients, for several days after a headache had been elicited the basal pulse and blood pressure levels were greater than they had been (Table 2).

Venous Phenomena. Concurrently, with the investigation of these headaches, observations were made upon venous reactions which appeared in some patients, regardless of whether or not headaches were present. It was found that where it was necessary to use small and superficial vessels, particularly those on the front of the wrist, to inject the adrenalin, transitory changes appeared in these veins. The changes took the form of the appearance, within about 10 minutes after injection, of white streaks which followed the course of the vein and often extended from four to five inches up the arm, with occasional branching out for shorter distances. In some instances the streak extended back from the point of injection for about $\frac{1}{2}$ inch, and in a few instances spread out from the sides of the streak in pool-like form, starting about 1 to 2 inches above the point of injection. In almost one-third of these cases, goose pimples appeared along the course of the white streaks. The goose pimples usually disappeared fairly soon after the injection, but the white streaks would persist as long as 5 hours. With subsequent injections of adrenalin at 10-minute intervals in the same vein, the streaks tended to

TABLE 2.—CONTINUANCE OF INCREASED REACTIVITY OF PULSE AND BLOOD PRESSURE ON FIFTH DAY AFTER APPEARANCE OF HEADACHE—SEE TABLE 1.

Miss N. S.		March 30, 1945.			
	Time	B. P.	Pulse	Remarks	
Initial recording . . .	2:10	138/90	88	No panic attacks in past week.	
1st injection					
1 min.	2:20	148/88	78	No headache.	
10 min.	144/90	84		
Amount 0.02 mg.					
2nd injection					
1 min.	2:32	156/84	75		
10 min.	136/80	84		
Amount 0.03 mg.					
3rd injection					
1 min.	2:45	152/84	84		
10 min.	140/70	80		
Amount 0.04 mg.					
4th injection					
1 min.	2:59	154/84	81		
10 min.	130/80	76		
Amount 0.01 mg.					

Note:—(i) Initial blood pressure and pulse substantially higher than before the headache on March 25, 1945. (Compare initial readings in Tables 1 and 2).

(ii) Blood pressure and pulse rise is now slightly greater in response to 0.02 mg. adrenalin hydrochloride than it was to 0.01 mg. (Contrast first injection on Table 1 with first injection on Table 2).

become more pronounced and to extend further.

It was found that the streaks could not be eliminated by producing passive venous congestion of the arm, save that their color became temporarily lost during the period that the arm was cyanosed, reappearing again as soon as the congestion had disappeared. They could, however, be eliminated entirely by injecting a solution of histamine hydrochloride, containing 0.1 mg. of the drug, for a few minutes into the vein which had been used for the adrenalin administration. There seemed to be no reason to doubt that the white streaks represented changes in the vein itself and in some of its branches. The pooling effect was less clear. It did not appear to be due to the leakage of adrenalin from the point of injection, since it usually occurred 1 to 2 inches above this. The appearance of goose pimples in the skin along the course of the vein suggested, however, that either a transudation of the solution from the vein might occur, or that there might be a radiation of its constrictor effect from the walls of the vein to those muscular structures lying outside it which control the appearance of goose pimples.

Discussion. Our attempts to assess the significance of these observations upon head and neck aches, upon cardiovascular reactivity and upon the venous phenomena consequent to the injection of amounts of adrenalin apparently excessive can only be tentative, since there are still many gaps in our information.

The issue of primary importance which emerges from these observations is that the effects of excessive adrenalin administration may persist long after its general pressor action has disappeared. The significance is derived from the possibility that it may advance our knowledge of the development of the chronic tensional anxiety states.

How far are the mechanisms involved in the 3 groups of observations related? The effects, as far as the veins are concerned, appear to consist in a spasm of

the muscle elements in their walls which may persist for several hours and, on occasion, may extend to the muscle structures of the overlying skin responsible for the production of goose pimples. This explanation is rendered the more probable by the fact that the goose pimples and the blanching can be completely abolished by the injection of histamine, which acts to relax muscular contraction in considerable areas of the cardiovascular system (Goodman and Gillman³).

The mechanisms involved in the head and neck aches appear to be more complex. It is necessary to consider not only the cause of these symptoms but also the explanation of their location. The fact that the headaches are at first primarily throbbing in character, that they appear coincidentally with excessive blood pressure rises and that they tend to disappear, though only transitorily, during the administration of histamine, suggests that they are vascular in origin and may be related to spasm of the arterial musculature. On the other hand, the fact that they tend to merge ultimately into an aching of the neck, and that they can be most readily overcome by heat and massage suggests that they may, at least in part, be due to spasm of skeletal muscle in those areas.

The question as to why these effects of activity should appear primarily in the occipital and neck regions is difficult. It may be said, however, that many tensional anxiety patients who have not received adrenalin complain in lesser degree of just such symptoms. It would appear that the scalp and the neck musculature are areas in which increased tension readily occurs. To this must be added the fact that they are areas subjected to frequent stimulation, the first through the participation of the scalp musculature in changes in emotional expression of the face, and the neck musculature through turning movements of the head.

Of still more importance is the fact that, in states of increased tension, the flexor musculature of the body tends to exert a

greater pull than the extensor. This produces the well known bowing of the back, bending at the knees and elbows and the bending forward of the neck. Hence the support of the head is thrown primarily upon the extensor musculature of the neck. Thus it is clear that, in the tensional anxiety cases, the musculature of the scalp and that of the back of the neck (which runs up for its attachment into the occipital area) are under special stress and for that reason may be presumed to be particularly likely to go into spasm when subjected to further sudden increase in tension, as during adrenalin administration.

The observation that, immediately following upon the administration of an excessive dose of adrenalin and in some instances for several days thereafter, the cardiovascular system reacts by the development of increased pressor response to further adrenalin administration and by increased basal blood pressure and pulse levels suggests that the reactivity of the muscle elements of the cardiovascular system has been increased.

Hence, it will be seen that the mechanism involved in all 3 groups of phenomena appears to be an increase in the reactivity of those muscle structures which ordinarily react to adrenalin. We have no evidence as to whether or not there is an increased reactivity of the other structures which react to adrenalin: of the secretory tissues and perhaps the central nervous system.

Here we wish to emphasize a point of fundamental importance, which, because our medical thinking is still dominated by the determinism of physics, we find it hard to keep steadily before us. Adrenalin, like any other agent, produces in the living organism an immediate reaction and may, as here, produce a change in the reactivity of the structures upon which it acts.

It is this increased reactivity which is of prime significance, in that it may afford us insight into the development of the chronic tensional anxiety reactions and the ultimate establishment of the auton-

omous anxiety state (Cameron^{2a}) which has analogies with the concept of "structuralization" of the repetitive neurotic mechanism (Kubie⁴).

We are already aware that patients suffering from these states are more reactive to the injection of adrenalin (Maranon,⁵ Backova,¹ Richter,⁶ Thorley⁷) and that such injections cause a transitory reactivation of many of their complaints, and by no means only those related to increased muscular tension, so that the patient will often comment anxiously that we have brought back all his symptoms (Cameron^{2e}).

Here, in these 7 patients, one sees that an excessive stimulation of the muscle structures which ordinarily react to adrenalin causes an increase in their reactivity which may persist over several days, and which, in one case in which the excessive stimulation was frequently repeated, persisted over a period of 43 days.

It seems reasonable to compare these findings with the situation which exists where the individual is exposed to repeated psychic traumata with repeated participation of the adreno-sympathetic system, such as occurs in combat experience or in prolonged involvement in a guilt or other conflict situation. In these situations, as in that presented in this report, there frequently results an increased reactivity of those structures which react to the adreno-sympathetic system. But these two situations differ in that the psychic traumata are repeated over long periods and lead, in a proportion of cases, to such a degree of increased reactivity of those structures which react to the adreno-sympathetic system that they eventually respond excessively to ordinary everyday stresses, thus resulting in the establishment of a self-perpetuating autonomous anxiety state (Cameron^{2a}).

In the cases presented in this report, stimulation was limited to a few occasions and no lasting increased reactivity resulted, though there is evidence in at least one case that repeated stimulation would result in more lasting increased reactivity.

Summary. Administration of excessive amounts of adrenalin may result in severe head and neck aches, in transitory blanching of the injected vein together with the appearance of goose pimples, and in the persistence for several days of an increased

pressor response to adrenalin. The mechanism of these symptoms is discussed and their relationship to the production of the chronic tensional anxiety state is considered.

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THIAMINE CIRCULATION TIME

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THE use of thiamine hydrochloride as a new method for the determination of the circulation time was the subject of a preliminary report.⁵ It was shown that the nut-like taste and smell of the drug gave arm-to-tongue or arm-to-nose circulation times in normal adults of 5 to 12 seconds. Since these values were much below others recorded in the literature,⁴ by the use of other subjective and objective methods (Table 1), the effects of dosage and volume upon the circulation time were also studied.⁷ The conclusions were that increasing doses speed the response until the "true" circulation time is reached (Fig. 1), and that thiamine gives shorter values, with optimal dosage of 100 to 300 mg. or more, than the maximum safe doses of magnesium sulphate, aminophylline, or decholin. Furthermore, volumes of solution 5 cc. or greater, which are often used clinically, as in the decholin method, have the mechanical effect of shortening the circulation time by 1 or more seconds.⁷ The purpose of this paper is to report the determinations of thiamine circulation time in 295 cases of various conditions and to discuss certain factors which affect the measurement of circulation time in general.

To eliminate the volume and dosage factors,⁷ all measurements were made with 1 cc., containing 300 mg. of thiamine hydrochloride,* injected rapidly intravenously, and timed from the beginning of the injection to the moment the subject first signified the taste or smell of the drug. Most patients tasted and smelled the drug simultaneously, but others noted taste or smell alone or one soon after the other.

On rare occasions the taste or smell recurred faintly, as from recirculation, or, on the other hand, as if the first quick faint end-point indicated arrival at the lungs with perception of the drug in the expired breath. Complete failure to taste or smell the drug occurred in 13 of 295 cases, and obviously false high readings, up to 120 seconds, occurred in 9 others, particularly in cases of congestive heart failure. Some of this group responded, with reasonably low readings, when the dosage was increased above 300 mg. up to 600 or 900 mg. (2 or 3 cc.), but they are not included in our data. Check determinations with magnesium sulphate or decholin were obtained in most cases and gave, on the average, readings 4 to 20 seconds longer, especially in heart failure, and about the same percentage of total failures.

Ninety-two normal adults tested by this method showed circulation times of 5 to 13 seconds, most of them 7 to 10 seconds (Fig. 2). Repeated determinations a few hours apart checked usually within 1 or 2 seconds. Post-prandial readings were little or no lower than fasting, but circulation times in the vertical position were usually 1 to 3 seconds shorter than in the horizontal.⁶ Complete failures in this group of normals occurred in 4 additional cases, and false high readings of 25 and 120 seconds in 2 others. Four of these 6 individuals were over 60 years of age. Seventeen normal children, aged 5 to 12, responded in 4 to 8 seconds.

Patients with heart disease were subdivided into 4 functional classes, according

* Specially prepared in 10-cc. vials by E. R. Squibb and Sons.

to the Criteria of the New York Heart Association, in tabulating the results (Fig. 2). Five children with rheumatic heart disease, but without congestive heart failure, had circulation times within normal limits, 4 to 8 seconds. In 1 child with severe congestive heart failure (Class IV), the circulation time was 15 seconds.

Sixty-five adults with organic heart disease but without congestive heart failure (Class I) had circulation times of 5 to 20 seconds, but only 4 of the 65 showed values beyond the normal limit of 13 seconds. It is quite possible, that these 4 patients were wrongly judged clinically to be in Class I instead of Class II. There was no apparent corre-

TABLE 1.—NORMAL CIRCULATION TIMES BY VARIOUS METHODS

Substance	Effect at	Circ. time (secs)	Authors
Diodrast	Left ventricle	6-9	Robb and Steinberg, 1938
Thiamine	Tongue and nose	5-13	Ruskin and Decherd, 1945
Lobeline	Carotid sinus	6-13*	Piccione and Boyd, 1941
Radioactive sodium	Other arm (children)	5-17	Hubbard et al, 1942
Fluorescein (ultraviolet)	Conjunctiva	7-15.6	Fishback, 1941
Calcium chloride	Tongue	9-15	Kahler, 1929
Magnesium sulphate	Tongue	7-17.8	Bernstein and Simkins, 1939
Saccharin	Tongue	9-16	Fishberg et al, 1935
Decholin	Tongue	10-16	Tarr et al, 1933
Calcium gluconate	Tongue	10-16	Goldberg, 1936
Aminophylline	Medulla	7.1-20.4	Koster and Sarnoff, 1943
Methylene blue (photoelect.)	Skin	7-21.6	Jablons et al, 1944
Phenoltetraiodophthalein	Femoral artery	10-18	Hamilton et al, 1932
Magnesium sulphate comp. (Macasol)	Tongue	5-21	Kvale and Allen, 1939
Sodium cyanide	Carotid sinus	9-21	Robb and Weiss, 1933
Thorium-X	Other arm	10-20	Gerlach et al, 1943
Radium-C	Other arm	12-23	Blumgart and Weiss, 1927
Fluorescein (ultraviolet)	Lip	15-20	Lange and Boyd, 1942
Papaverine	Medulla	15.4-27	Elek and Solarz, 1942
Histamine	Skin	13-30	Weiss et al, 1929

* Add a minimum of 1 second for injection time.

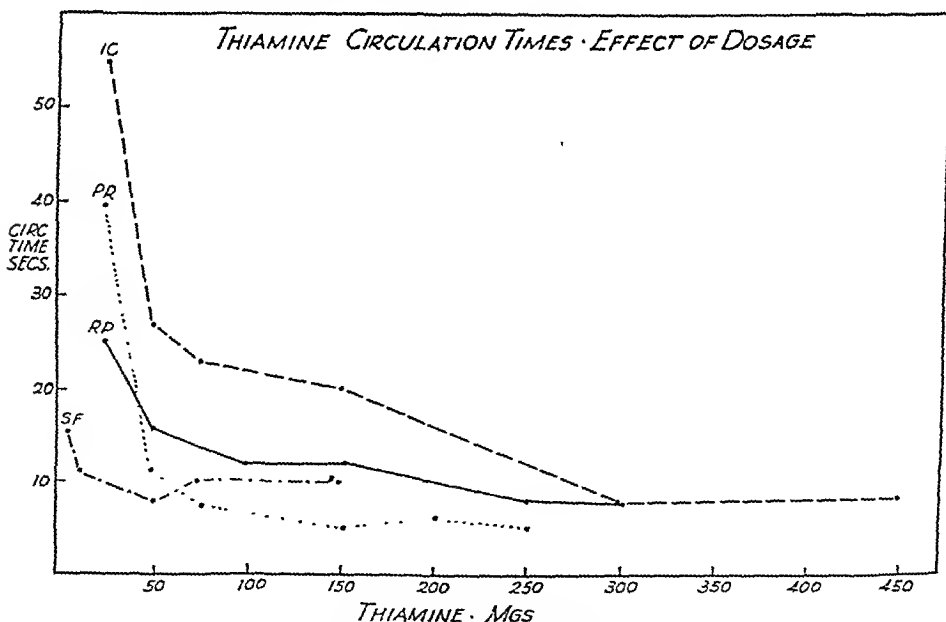


FIG. 1.—Curves showing the effect of increasing doses of thiamine upon the circulation times of 4 normal individuals.

lation between circulation time and roentgenographic evidence of enlargement of the heart in this group, contrary to Nylin.³ Thirty-one patients in mild (Class II) failure had circulation times of 8 to 25 seconds; 23 in moderate (Class III) failure, 10 to 50 seconds; 17 in severe (Class IV) failure, 13 to 55 seconds. There were 2

other words, some cases of predominant left heart failure may be expected to show circulation time values considerably longer than those of right heart failure alone.

Five cases in moderate or severe congestive failure given 1.2 mg. of digitoxin by mouth, were tested every 2 to 3 hours and showed the first definite lowering of

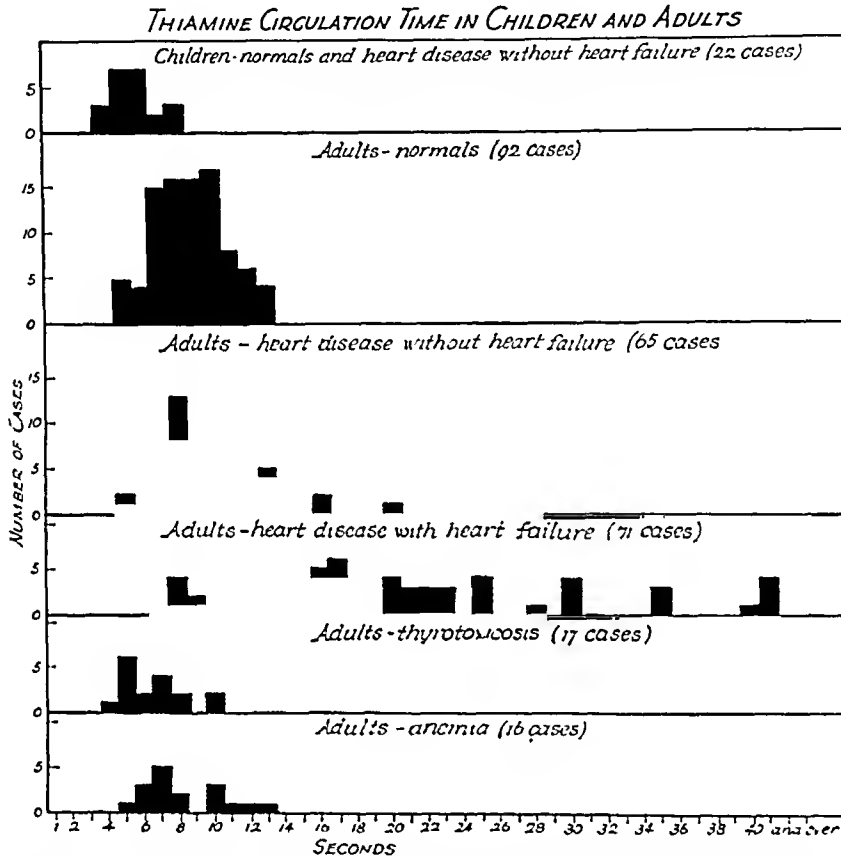


FIG. 2.—The circulation times in various patients, with and without heart disease, obtained by the injection of 300 mg. of thiamine hydrochloride.

outstanding exceptions; one case of marked emphysema and another of old hypertensive heart disease, both in severe right heart failure without any pulmonary congestion. Each had a circulation time of 7 seconds. Other cases of cor pulmonale, including those in whom systemic venous congestion had superseded pulmonary congestion, account for many of the lower values in the entire congestive failure group. Considering that the pathway of any drug employed to measure the "total" circulation time involves the small vessel circuit in the lungs and not in the periphery, these results are not surprising. In

the circulation time (by 3 or more seconds) in 4, 7, 9, 10 and 12 hours, respectively. This increased rapidity of blood flow is presumably to be correlated with the expected increase in cardiac output and in the first signs of improvement in the patient's functional status.

The effect of exercise up to the point of dyspnea, using the Master two-step equipment, tended to reduce the circulation time 1 to 3 seconds both in normal individuals and those presenting various degrees of congestive heart failure. There were no instances of significant prolongation after exercise in either group. The

attempt to distinguish early congestive failure from other conditions producing subjective dyspnea by means of the effect of exercise upon the circulation time would thus appear to be doomed to failure.

Nine cases of anasarca due to cirrhosis of the liver or nephrosis had normal circulation times of 7 to 13 seconds. Sixteen cases of moderate to severe anemia of various origins had circulation times of 5 to 13 seconds, the majority being 6 to 8 seconds. One case of sickle cell anemia with moderate congestive heart failure responded in 7 seconds, as did another, who in a previous crisis without heart failure had a circulation time of 5 seconds. There was no apparent correlation between the degree of anemia and rapidity of blood flow. Seventeen cases of thyrotoxicosis presented the expected accelerated circulation times of 4 to 10 seconds, 12 of them being 5 to 7 seconds. Again there was no correlation between the basal metabolic rate and circulation rate. Two cases of moderate (treated) myxedema had circulation times of 12 seconds. Two cases of high fever responded in 6 and 7 seconds respectively.

Comment. For more complete discussion, the reader is referred to one of our previous papers on the subject.⁷ In view of the widespread measurement of the circulation time, especially as a method of diagnosing and following-up cases of congestive heart failure, certain points require particular emphasis. First, the usual doses of magnesium sulphate, calcium gluconate, and decholin used in clinical practice, may, and frequently do, give false high readings of the circulation time. That may be true even of 1-gram doses of magnesium or calcium salts. It has been common experience to get faint pharyngeal burning following the injection of one of these drugs in as long as 60 to 150 seconds, values that are obviously too high even for severe congestive heart failure. When large volumes of solution are used, the error may be the other way, that is, toward a quicker response.

Second, the so-called objective methods, involving the detection of dyes, radioactive substances and deepening of respiration, also give "normal" readings that are much too high (Table 1) and need restudy from the standpoint of the influence of dosage, volume and, perhaps, other unknown factors, before valid acceptance clinically. Furthermore, when these methods are applied to the study of peripheral arterial or venous obstruction, or congestive heart failure, that is, where either slowed blood flow or long circuitous pathways are involved, false high readings are again to be guarded against. Our own experiences⁶ with the objective methods involving the production of the inspiratory gasp have been disappointing in the high incidence of total failures and indefinite and false high readings. That has been particularly true of the aminophylline method, the papaverine method,¹ and the use of nikethamide.

Nikethamide, one of the better known respiratory stimulants, can be used in a dose of 3 cc. of the 25% solution* intravenously as a measure of the circulation time, particularly in children.⁷ The inspiratory gasp and, at times, a subjective burning of the face, occur in 6 to 9 seconds in children and in 7 to 12 seconds in most adults. However, in a total of 69 cases, 10 failures to obtain a clear end-point and 5 false high readings were encountered. The failures occurred particularly in cases of congestive heart failure, in which the drug would have been most useful, so that the method was abandoned.

The ideal method for the measurement of the speed of blood flow should be simple, objective, safe, and exact; this is yet to be found. The thiamine method has the disadvantage of requiring the cooperation of the subject and the injection of rather large doses of the drug. It has the advantages of simplicity, safety, and exactness. In case of failure to respond to the 300-mg. dose, 600, 900 mg. and even larger doses may be safely injected. To prevent another failure or delay in

* Generously supplied to us by Lakeside Labs., Milwaukee, Wis.

response, an interval of at least 2 hours between injections has been found satisfactory.⁷ Oral medication of thiamine or brewer's yeast and the fetor of suppurative bronchopulmonary disease have not affected the taste and smell of the injected thiamine in our subjects.⁶ No serious allergic or anaphylactic reactions to the drug have been encountered by us in more than a thousand injections, except one case of mild urticaria in a person who had received therapeutic injections of "Betalin" a few months previously. A few serious reactions have, however, been recorded in the literature, including 2 deaths ascribed to repeated intravenous use of the drug.² Some reports of toxic reactions have emphasized the importance of a preliminary skin test as well as the avoidance of an interval of 1 or 2 weeks between injections as prophylactic measures.

Summary and Conclusions. 1. Thiamine hydrochloride, in a standard supra-optimal dose of 300 mg., is a safe and more exact subjective method for determining the speed of blood flow from arm to tongue.

2. The normal circulation time by this method is 4 to 8 seconds in children and 5 to 13 seconds in adults. Studies have been made in 295 different cases, and values recorded for various grades of congestive heart failure and other disorders.

3. Circulation time by any clinically used method varies inversely with the dosage of the drug until a point is reached which may be called the true or shortest circulation time.

4. This point is usually reached at a dose level of 200 to 300 mg. of thiamine, and may not be reached at the maximum safe dosage of 1 gram of magnesium sulphate, 0.48 gm. of aminophylline, or 5 cc. of 20% decholin.

5. Another source of error in doing circulation times with volumes of solution 5 cc. or greater is the shortening apparently resulting from the rapid injection of these amounts under pressure.

6. The ideal method for determination of circulation time should be simple, objective, safe, reproducible, and one employing constant dosage, which would be supra-optimal for all individuals. Such a method is yet to be found.

ADDENDUM: Since the submission of this paper an unknown component of vitamin B complex (Swenson, R. E.: *Am. Heart J.*, 32, 612, 1946) has been proposed as resulting in a characteristic taste which makes it useful as a method of arm-to-tongue circulation time. This substance, as indicated in this and our previous paper, is probably thiamine.

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THE ELECTROCARDIOGRAPHIC CHANGES CAUSED BY HYPERVENTILATION

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SINCE the observations by Vandell Henderson that hyperventilation induces circulatory and neurologic disturbances due to the hypocapnia and gaseous alkalosis, numerous reports on the effect of hyperventilation on the electrocardiogram have appeared.^{4,7,8,9,10,16} These electrocardiographic alterations were usually attributed to the chemical changes provoked by overventilation.

However, it has been observed that alkalosis may be present without the appearance of alteration of the waves in the electrocardiogram and conversely that significant electrocardiographic changes may be present without alkalosis;¹⁶ moreover, no parallelism need exist between the degree of the electrocardiographic changes and the extent of the alkalosis.⁴

In view of these discrepancies, we decided to re-investigate the influence of hyperventilation on the electrocardiogram. This seems to have practical importance since hyperventilation is not an uncommon event in patients whose electrocardiogram is taken, especially when pain and anxiety connected with cardiac disease are present. The fear of electricity is widespread and frightened patients may hyperventilate during the application of the electrodes. Furthermore, alkalosis does occur in manifold conditions; an example is the alkalosis following the ingestion of large doses of alkali. The changes in the electrocardiogram attributed to alkalosis were in some reports rather striking and an awareness of these changes is necessary if confusion with the abnormalities due to intrinsic cardiac disorders is to be avoided.

Method of Study. All subjects were hospitalized medical patients who showed

neither clinical nor electrocardiographic evidence of cardiac disease. All lay quietly and flat in bed during the examination in order to eliminate positional effects on the electrocardiogram. Four types of experiments were performed: 1. Hyperventilation was done by means of slow and deep respiratory excursions which did not produce tetany or alkalosis. The respiratory rate averaged 10 per minute and this type of breathing was continued for 3 minutes. The carbon dioxide combining power was obtained before and after hyperventilation on most of these patients. This was done on venous oxalated blood by the Van Slyke gas analysis method.

2. Hyperventilation was performed by means of rapid and deep respirations until tetany and alkalosis were produced. The respiratory rate averaged 30 per minute and was kept up at this rate for 5 to 15 minutes until symptoms of tetany appeared.

Determinations of the pH of the blood were made on 10 successive patients. This was done on venous blood serum, collected under oil and centrifuged at a high speed for 5 minutes. Calculations were done by means of a Cambridge cathode electron ray pH meter with a McGuinness electrode.

3. The patient was ordered to perform very shallow and very rapid respirations, averaging 100 per minute, for 2 to 3 minutes. The breathing was of the costal type, predominantly.

4. The breath was held in forced inspiration and in forced expiration. The patients were permitted to breathe between the taking of the different electrocardiographic leads so that the apneic period did not last more than 5 to 15 seconds.

Control electrocardiograms were taken before the experiments, and repeated during the period of overventilation when signs of tetany had appeared and 10 minutes after hyperventilation had ceased. Each tracing was so standardized that corrections for amplitude were not necessary and unimportant.

Fifty-two patients were subjected to 89 experiments; 13 of these patients (as indicated by an asterisk in Tables 2, 3 and 4) were subjected to 3 types of experiments: hyperventilation tetany, rapid and shallow respirations, and forced inspirations and forced expirations. These procedures were done during the same experimental period.

Results. 1. **HYPERVENTILATION WITHOUT THE PRODUCTION OF TETANY.** Sixteen males and 1 female were subjected to this procedure. Their ages varied between 24 and 46 years (Table 1).

(or a diminished inversion) occurred 7 times and a decrease of the T wave appeared once. In 7 instances, no changes were registered. In 1 case, the inverted T wave in Lead 3 became upright and in another the inverted T wave became more negative.

Thus in most cases the R and T waves in Lead 1 became smaller while those in Lead 3 became taller.

A study of Table 1 reveals that no correlation existed between the changes in

TABLE 1.—THE EFFECT OF HYPERVENTILATION WITHOUT TETANY UPON THE R AND T WAVES OF THE ECG

No. and name	Age	Sex	Diagnosis	CO ₂ combining (vols. %)		R waves (mv.)			T waves (mv.)		
				Before	After	Lead 1	Lead 2	Lead 3	Lead 1	Lead 2	Lead 3
1. R. M.	28	M	Neurosis	64	53	-0.1	+0.05	0	-0.1	-0.1	0
2. C. S.	32	M	URI*	67	60	-0.1	+0.2	+0.25	0	+0.1	+0.1
3. E. D.	45	M	Peptic ulcer	60	52	-0.2	-0.5	+0.15	+0.15	+0.05	0
4. H. H.	35	M	Neuritis	-0.2	-0.1	+0.15	-0.1	-0.05	+0.15
5. C. M.	46	M	URI	64	53	-0.1	0	+0.15	-0.15	-0.15	0
6. C. T.	34	M	URI	66	58	-0.1	-0.1	0	-0.05	-0.0250	0
7. G. C.	40	M	Pulm. tb.	+0.25	-0.15	-0.1	+0.125	-0.025	-0.1
8. M. G.	46	M	Peptic ulcer	62	52	-0.25	-0.2	+0.1	0	0	I to U
9. M. M.	38	M	Bronchitis	66	56	0	0	0	0	+0.05	+0.05
10. W. O.	43	M	Peptic ulcer	-0.1	0	+0.1	-0.1	0	+0.1
11. E. G.	28	M	Bronchitis	61	51	-0.2	-0.1	+0.1	0	0	I to +I
12. J. F.	46	M	Neurosis	61	58	-0.05	-0.05	0	0	0	0
13. R. V.	24	M	Parasitic infection	58	45	-0.1	-0.2	-0.1	-0.1	0	+0.05
14. M. S.	37	M	Neurosis	-0.15	0	+0.15	-0.1	0	+0.1
15. R. S.	30	F	Gastritis	-0.1	0	+0.1	-0.15	-0.15	0
16. A. A.	24	M	URI	64	55	+0.1	0	-0.1	0	+0.05	+0.05
17. M. S.	38	M	Peptic ulcer	-0.15	0	+0.15	0	0	0

+ = increase in amplitude; - = decrease in amplitude; 0 = no change; I = inversion of wave; U = uprighting of wave; I to +I = increase in inversion; I to -I = decrease in inversion; D = diphasic.

* Upper respiratory infection.

The R wave in Lead 1 decreased in 15 of the 17 patients. The replacement of an R wave by an S wave did not occur and if an S wave was present it did not become deeper. In 1 patient, the R wave became taller in Lead 1 and in 1 it remained unchanged. In Lead 3, the R wave became taller or the S wave shorter in 10 instances. The R wave became shorter in Lead 3 in 3 patients and 4 times there was no change. Therefore, there was a distinct tendency to right axis deviation. In no instance was there a deviation of the RS-T segment.

The T waves in Lead 1 became lower in 8 cases and in 2 it was higher. The greatest decrease was 0.15 mv. and the greatest increase amounted to 0.125 mv. In Lead 3 an increase in the height of the T wave

the R waves and the changes in the T waves. At times when the R waves changed their height definitely, the T waves remained unaltered or a lower R wave was followed by a higher T wave.

The carbon dioxide combining power was done in 11 of the patients of this group, before and at the end of the hyperventilation. In all cases there was a shift to the acid side without the production of a true acidosis. Compensatory mechanisms were apparently active which not only corrected the effect of the loss of carbon dioxide but led to a slight overcompensation. Barker obtained similar results.⁴

2. **HYPERVENTILATION WITH THE PRODUCTION OF TETANY AND ALKALOSIS.** This experiment was done with 35 patients,

12 females and 23 males (Table 2). The ages of the patients varied from 14 to 60 years. The blood pH was determined in the first 10 patients. The values before hyperventilation varied between 7.35 to 7.60 and those after hyperventilation ranged from 7.53 to 7.77.

Twenty-four patients showed a decrease in the amplitude of the R wave in Lead 1 after hyperventilation; an increase was found in 2 instances and 9 subjects showed no change. A decrease of the R wave or a deepening of the S wave occurred 6 times, whereas 13 patients showed an increase of the R wave or a shortening of the S wave in Lead 3. In 16 cases, the QRS complexes remained unchanged in Lead 3.

The T waves in Lead 1 were decreased in 20 instances; no changes occurred in 1 patient and in 14 the T waves became higher. A decrease in the amplitude of the T wave was observed 6 times in

Lead 3, an increase occurred in 15 patients and in 14 instances no changes appeared.

Again, the majority of the cases showed a lowering of the R and T waves in Lead 1 while those in Lead 3 became higher.

Figure 1, *A* and *B*, shows the tracings in the 3 limb leads of Patient 7 of Table 2 before and after hyperventilation. There is a significant lowering of the R waves and T waves in Leads 1 and 2 and marked increase of the R waves in Lead 3. Figure 1, *C*, shows the return to the normal picture after 10 minutes. The changes in Figure 1 were the most pronounced obtained in our experiments.

No correlation could be discovered between the shift of the blood pH and the changes in the electrocardiogram. Patients who showed the greatest shift of the pH might exhibit little or no change in the electrocardiogram.

3. RAPID AND SHALLOW BREATHING. Very rapid and shallow breathing, averaging 100 respirations per minute, was done

TABLE 2.—THE EFFECT OF HYPERVENTILATION WITH TETANY UPON THE R AND T WAVES OF THE ECG

No and name	Age	Sex	Diagnosis	Blood Ph		R. waves (Millivolts)			T waves (Millivolts)		
				Before	After	Lead 1	Lead 2	Lead 3	Lead 1	Lead 2	Lead 3
1 G R.*	17	F	Pneumonia	7.39	7.55	-0.05	+0.10	+0.15	0	0	0
2 Y Y.*	26	F	Nephrosis	7.35	7.53	+0.1	0	0	0	0	0
3 G W.*	22	F	URI	7.47	7.54	0	0	0	0	0	0
4 S S.*	28	M	URI	7.48	7.77	-0.05	-0.05	0	-0.10	-0.20	-0.05
5 F. D.*	50	M	Diabetes	7.56	7.70	-0.15	0	+0.15	0	0	0
6 A B.*	13	M	URI	7.47	7.65	-0.25	+0.30	+0.50	-0.1	-0.2	U to D
7. J K.*	28	M	Malaria	7.58	7.65	-0.2	-0.1	+0.1	0	-0.02	0
8 V C.*	18	M	Rheumatism	7.58	7.74	-0.1	0	0	-0.05	-0.05	0
9 T B.*	41	M	Anemia	7.54	7.71	-0.1	-0.1	0	-0.02	0	0
10 R C.*	20	M	URI	7.60	7.67	0	0	0	-0.05	0	0
11 J P.*	25	M	URI	.	..	-0.1	-0.1	0	0	0	0
12 J S.	14	M	URI	.	..	0	0	0	0	+0.075	+0.075
13 A S.	37	M	Grippe	-0.2	+0.1	+0.3	-0.05	-0.1	-0.025
14. M G.	14	F	Bronchitis	-0.05	-0.2	-0.15	0	0	0
15 L O.	29	F	Neurosis	-0.1	-0.1	0	-0.05	0	+0.05
16 R P.	28	F	Pleurisy	0	0	0	0	+0.05	1 to -1
17 C V.	52	M	Peptic ulcer	0	0	0	-0.05	0	+0.05
18 J W.	34	M	Bronchitis	+0.125	0	-0.1	+0.025	0	-0.025
19 A V.	52	M	Alcoholism	-0.1	-0.1	0	-0.02	-0.05	-0.025
20 F M.	47	M	Pulm th	-0.05	-0.2	-0.15	-0.025	0	+0.05
21 T H.*	27	M	Malaria	-0.4	0	+0.4	0	U to I	I to +I
22 A C.*	58	M	G I cancer	0	0	0	-0.025	-0.02	0
23 J V.	52	M	Peptic ulcer	-0.025	-0.1	-0.1	0	+0.02	0 to 0.75
24 E R.	45	F	Neurosis	-0.1	-0.025	+0.1	0	0	0
25 S T.	23	F	URI	0	+0.1	+0.1	0	+0.025	0
26 M. C.	14	F	Bronchitis	-0.05	0	+0.05	-0.1	-0.1	0
27 I. N.	23	F	Asthma	-0.05	-0.15	-0.15	-0.025	0	+0.02
28 R. L.	45	F	Epilepsy	-0.2	0	+0.2	-0.05	-0.075	I to U
29 H B.	60	F	Neurosis	0	0	0	0	0	0
30 S P.	54	M	Pneumonia	-0.3	+0.05	+0.25	-0.05	0	+0.05
31 K. G.	55	M	Brain tumor	-0.15	-0.05	+0.1	-0.05	0	+0.05
32 R G.	16	M	Pneumonia	0	0	0	-0.05	-0.05	D to U
33 N S.	25	M	Pneumonia	-0.05	0	0	-0.1	-0.15	-0.05
34 E. T.	46	M	Pneumonia	-0.1	0	+0.1	-0.05	0	+0.05
35. L. K.*	20	M	Atelectasis	-0.1	-0.15	-0.05	-0.1	-0.1	I to -I

by 11 patients (Table 3). Their ages varied between 13 and 50 years.

The R waves in Lead 1 became lower in 6 instances; in 2 it became higher and in 3 patients it remained unchanged. The R waves in Lead 3 showed an increase in amplitude in 6 patients and in 5 it did not change. Figure 1, *D*, obtained in the same experiment as Figure 1, *A* to *C*, shows that the alterations in the electrocardiogram are the same in both procedures.

The T waves in Lead 1 became smaller in 4 patients and were unchanged in 7.

Only in 1 case did the T waves become taller in Lead 3, the other 10 patients showing no change.

4. FORCED INSPIRATION AND FORCED EXPIRATION. Of 13 patients in this group, 3 were females. Their ages ranged from 13 to 50 years (Table 4).

Forced Inspiration. The R waves in Lead 1 became smaller in 7 instances and showed no change in 4. No increase occurred in the amplitude of the R wave in Lead 1 in 2 patients. The R wave in Lead 3 showed an increase in height in

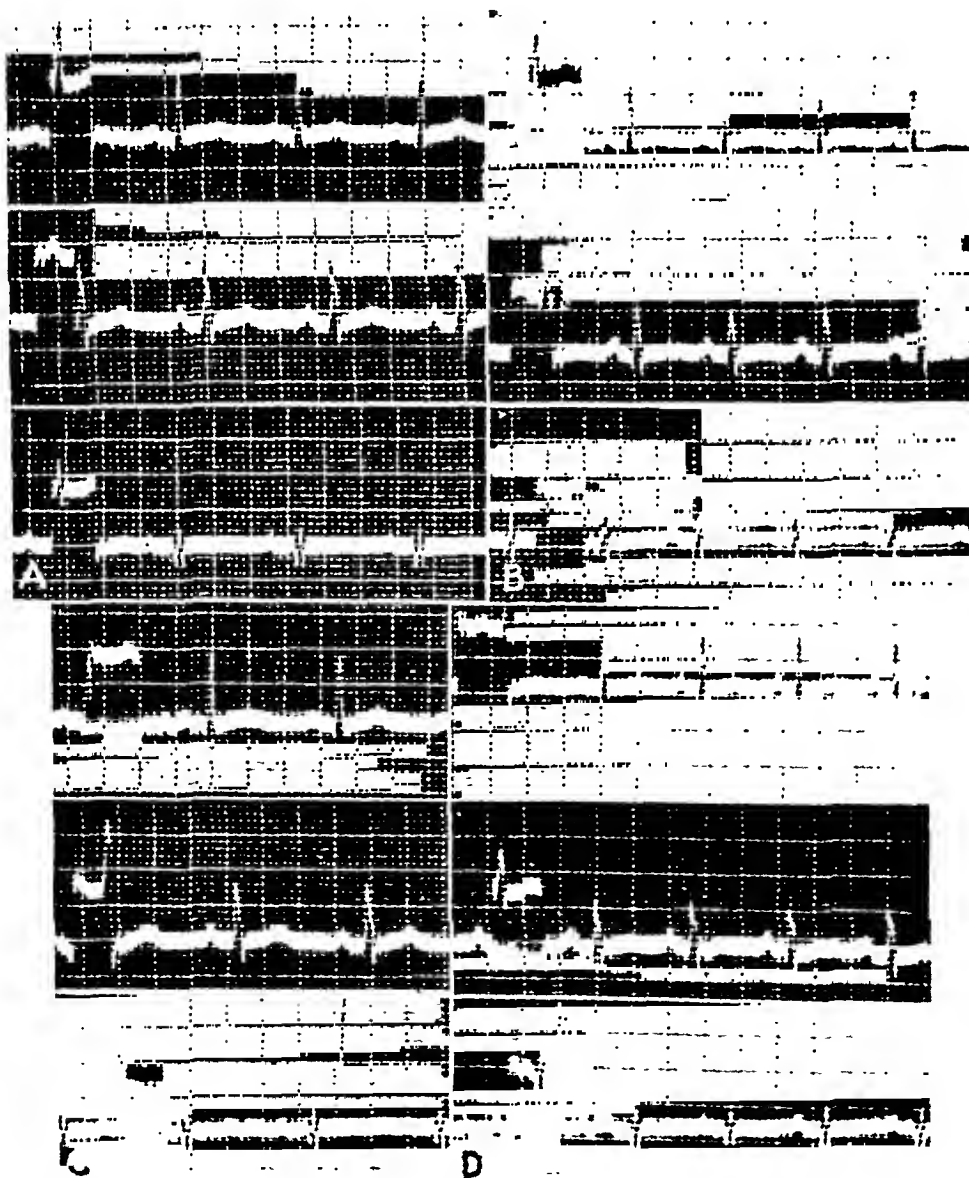


FIG. 1.—Electrocardiogram in standard leads before (*A*) and after (*B*) hyperventilation which caused tetany and alkalosis. *C* shows the electrocardiogram obtained 10 minutes after the hyperventilation. *D* was obtained after 5 minutes of rapid and shallow breathing.

4 patients. Six subjects presented a smaller R wave in the same lead and in 2 they remained unchanged.

The T waves in Lead 1 became smaller in 9 patients and in 2 they remained unchanged. An increase in the height of the T waves in Lead 1 did not occur in any of these patients. In Lead 3 the T waves were taller in 6 patients and remained unchanged in 2 patients. No decrease in amplitude occurred in any of these subjects. In Patient 2 the T wave in Lead 3 became less inverted while in

The T waves in Lead 1 did not change in 9 patients. There was a decrease in height in 3 and an increase did not occur in any. The T waves in Lead 3 remained unchanged in 7 patients and became taller in 2. A decrease in amplitude did not occur. Patient 2 showed an increase in the inversion of the T wave in Lead 3, whereas in Patient 5 the T wave in Lead 3 changed from diphasic to upright. A change from an inverted T wave in Lead 3 to a diphasic wave occurred in Patient 11.

The changes obtained in deep expiration

TABLE 3.—THE EFFECT OF RAPID AND SHALLOW BREATHING UPON THE R AND T WAVES OF THE ECG

No. and name	Age	Sex	Diagnosis	R waves (mv.)			T waves (mv.)		
				Lead 1	Lead 2	Lead 3	Lead 1	Lead 2	Lead 3
1. J. P.*	25	M	URI	-0.1	-0.05	-0.05	0	-0.25	-0.25
2. Y. Y.*	26	F	Nephrosis	+0.1	+0.05	0	0	0	0
3. G. R.*	17	F	Pneumonia	0	+0.05	+0.1	-0.5	+0.5	+0.5
4. G. W.*	22	F	URI	-1.5	-1.0	+0.15	0	-0.5	0
5. F. D.*	50	M	Diabetes	0	0	0	0	+0.5	0
6. A. B.*	13	M	URI	-0.2	-0.1	+0.15	-0.5	0	0
7. S. S.*	28	M	URI	-0.1	0	+0.1	-0.1	-1.5	0
8. J. K.*	28	M	Malaria	-0.1	0	+0.1	-0.5	-0.5	0
9. V. C.*	18	M	Rheumatism	-0.2	+0.15	..	-0.1	-0.05	0
10. T. R.*	41	M	Anemia	0	+0.05	+0.1	0	0	0
11. R. C.*	20	M	URI	+0.1	+0.05	0	0	0	0

TABLE 4.—THE EFFECT OF FORCED INSPIRATION AND EXPIRATION UPON THE R AND T WAVES OF THE ECG

No. and name	Age	Sex	Forced inspiration						Forced expiration					
			R waves (mv.)			T waves (mv.)			R waves (mv.)			T waves (mv.)		
			Lead 1	Lead 2	Lead 3	Lead 1	Lead 2	Lead 3	Lead 1	Lead 2	Lead 3	Lead 1	Lead 2	Lead 3
1. J. P.*	25	M	-0.25	-0.15	+0.1	-0.15	-0.1	+0.05	0	-0.2	-0.05	0	-0.1	0
2. L. K.*	20	M	-0.25	-0.3	-0.05	-0.2	-0.05	I to -I	-0.15	-0.3	-0.15	-0.05	-0.05 I to +I	+I
3. T. H.*	27	M	..	-0.05	-0.05	-0.05	..	0	0	0
4. Y. Y.*	26	F	0	+0.15	0	-0.05	0	+0.05	+0.05	+0.1	+0.05	0	0	0
5. G. R.	17	F	0	+0.15	0	-0.05	+0.025	+0.025	-0.05	+0.1	0	-0.075	+0.05 D to U	U
6. G. W.*	22	F	-0.075	-0.075	0	0	-0.075	I to +I	+0.1	+0.1	-0.25	0	0	0
7. F. D.*	50	M	-0.20	0	-0.15	0	+0.05	+0.05	+0.05	-0.05	0	0	+0.05	0
8. A. B.*	13	M	-0.35	+0.35	+0.70	-0.075	0	+0.075	-0.1	-0.1	0	0	0	0
9. S. S.*	28	M	-0.15	-0.05	+0.25	-0.15	-0.1	+0.05	0	+0.05	+0.4	-0.05	0	+0.05
10. J. K.*	25	M	+0.15	-0.1	0	0	0	+0.05
11. V. C.*	18	M	-0.075	+0.1	+0.2	-0.1	-0.05	I to U	-0.1	+0.1	0	0	+0.05 I to D	D
12. T. B.*	41	M	0	+0.1	+0.1	-0.05	0	0	0	+0.05	0	0	0	0
13. R. C.*	20	M	0	-0.1	0	-0.05	0	0	0	0	0	0	0	0

Patient 6 it became more inverted. In Patient 11 the T wave in Lead 3 changed from an inverted wave to an upright one.

Forced Expiration. Four patients responded with a decrease in the amplitude of the R wave in Lead 1, 4 with an increase and in 4 the wave remained unchanged. The R wave in Lead 3 became smaller in 3 records, remained unchanged in 7 and exhibited an increase in amplitude in 2 of the patients.

were less extensive than those shown by deep inspiration.

The data obtained in all experiments are summarized in Table 5.

Discussion. From the data presented in the preceding section, one may conclude that smaller changes of the R and T waves were obtained in all 4 series of experiments. These changes were independent of the presence of an alkaline shift in the blood serum and independent

of the signs and symptoms of tetany. The changes were identical whether the hyperventilation consisted of rapid and shallow breathing, rapid and deep breathing, or of slow and deep breathing. The abnormal deviations of the electrocardiogram appeared as early as 3 minutes after the beginning of hyperventilation and returned to normal within 10 minutes after hyperventilation had ceased.

those found in spontaneous hyperventilation.¹⁵ We can safely assume that patients exposed to heat which raises the body temperature to 104° F. do not have a peripheral vasoconstriction. Furthermore it is doubtful that hyperventilation under these conditions will produce an alkalosis. The basal metabolic rate is so much elevated at a temperature of 104° F. that the acid end products of the accelerated

TABLE 5.—COMPOSITE ANALYSIS OF THE RESULTS

Hyperventilation *without* tetany—17 patients:

R_1 { Decreased —15 Increased — 1 No change— 1	R_3 { Decreased — 3 Increased —10 No change— 4	T_1 { Decreased —8 Increased —2 No change—7	T_3 { Decreased —1 Increased —7 No change—7 1 to U —1 1 to +1 —1
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Hyperventilation *with* tetany—35 patients:

R_1 { Decreased —24 Increased — 2 No change— 9	R_3 { Decreased — 6 Increased —13 No change—16	T_1 { Decreased —20 Increased —14 No change— 1	T_3 { Decreased — 6 Increased —15 No change—14
--	--	--	--

Rapid and shallow breathing—11 patients:

R_1 { Decreased —6 Increased —2 No change—3	R_3 { Decreased —0 Increased —6 No change—5	T_1 { Decreased —4 Increased —0 No change—7	T_3 { Decreased — 0 Increased — 1 No change—10
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Forced inspiration—13 patients:

R_1 { Decreased —7 Increased —0 No change—4	T_1 { Decreased —9 Increased —0 No change—2
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R_3 { Decreased —6 Increased —4 No change—2	T_3 { Decreased —0 Increased —6 No change—2 1 to —1 —1 1 to +1 —1 1 to U —1
---	--

Forced expiration—13 patients:

R_1 { Decreased —4 Increased —4 No change—4	T_1 { Decreased —3 Increased —0 No change—9
---	---

R_3 { Decreased —3 Increased —2 No change—7	T_3 { Decreased —0 Increased —2 No change—7 1 to +1 —1 D to U —1 I to D —1
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The lack of proportional relationship between the shift of the blood pH to the more alkaline side and the electrocardiographic changes makes the explanation of the electrocardiographic findings by alkalosis unlikely.

Some investigators have found that hyperventilation with hypocapnia causes a marked peripheral and cerebral vasoconstriction.^{5,6} Because of these findings, a coronary vasoconstriction with consequent myocardial ischemia has been assumed to explain the changes in the electrocardiogram.^{3,16} However, it has been shown that patients placed in a Kettering hypertherm will hyperventilate and show electrocardiographic changes similar to

tissue metabolism will more than compensate for any loss of carbon dioxide which occurs during hyperventilation.

Finally, it is established that one of the earliest signs of anoxia of the heart muscle is a depression of the RS-T segments in Leads 1 and 2. This is due to the great sensitivity of the inner layers of the myocardium to ischemia. These subendocardial layers are the first to suffer if the blood supply to the heart is diminished. In all of our experiments, a depression of the RS-T segment was absent.

These facts would seem to invalidate both the chemical and vascular changes as a cause for the changes in the electrocardiogram following hyperventilation.

The observation that the inhalation of a mixture containing 5% CO₂ and 95% O₂ will immediately relieve the symptoms of hyperventilation tetany and cause the abnormal electrocardiographic changes to revert to normal,¹⁶ is no proof that the deviations found in the electrocardiogram are due to a loss of CO₂ and consequent gaseous alkalosis. It has been shown that the above gas mixture will cause an increase in the height of the T waves, less inversion of an inverted T wave and the uprighting of a diphasic T wave in cardiac patients without hyperventilation being performed. Patients with normal hearts also showed an increase in the amplitude of the T waves.²

The changes in the electrocardiogram caused by hyperventilation with or without tetany and alkalosis were the same as those which appeared when the electrocardiogram was taken during forced inspiration. It has been demonstrated that this positional change of the diaphragm leads to an alteration of the R and T waves which indicates a rotation of the electrical axis to the right.^{1,13,18} This change was not obtained in every individual during deep inspiration, for it depends on whether the heart rotates around its longitudinal axis or around an antero-posterior axis, or whether the heart simply moves with the diaphragm without any rotation.

Because of the striking similarity in the changes obtained in all 4 sets of experiments, we feel justified in assuming that the changes produced in hyperventilation were also chiefly caused by a change in diaphragmatic position. It is a well-known fact that overbreathing due to any cause leads to a more inspiratory position of the diaphragm which gradually subsides within a short time after overventilation has ceased.

Lowering of the T waves in Lead 1 also has been observed after exercise in normal individuals with healthy hearts.¹⁹ This has been confirmed in the laboratory of one of us and has been explained by a more inspiratory position of the diaphragm.¹¹ The lowering of the T waves

in Lead 1 after exercise has not rarely been interpreted as being due to coronary artery disease. Exercise as well as any increase in heart rate decrease the ventricular gradient.¹

Depression of the RS-T segment did not occur in any of our experiments. This is contrary to the experience of other authors who obtained such changes. Only where hyperventilation produced a marked tachycardia did a depression of the RS-T segments in Leads 1 and 2 occur. However, this is a regular finding in tachycardia, whether it is produced by exercise or the administration of atropine or amyl nitrite. This deviation can be attributed to the abnormal depolarization of the inner layers of the myocardium which occurs with an increase in heart rate. The tachycardias obtained by some authors during the hyperventilation was the simple consequence of the physical effort of this procedure.

In some instances the shallow and very rapid breathing may lead to a real anoxia of the myocardium. In this type of breathing the volume of tidal air is reduced to a degree where it surpasses but little the volume of air necessary to fill the dead space, and the exchange of gases suffers.

An inversion of the T waves in Lead 1 did not occur in any of our experiments, although its occurrence in Leads 2 and 3 is common due to a positional change of the heart.^{1,13,14,18} The marked immediate T wave changes and the late inversion of the T waves which were observed by Thompson were most probably due to the presence of coronary artery disease, which possibility was even discussed by the author. Hyperventilation in these cases had the same effect as an exercise test. In favor of this belief is the fact that in some patients these abnormally inverted T waves later became temporarily more positive than even the control T waves.¹⁵ This is a well-known after-effect of physical exercise in patients with coronary artery disease.¹² The mechanism involved is similar to that which causes the inver-

sion of the T waves after damage to the external layers of the myocardium (pericarditis) after the elevation of the RS-T segments has subsided.

In recent times even the electrocardiographic changes found in women with the climacteric syndrome and endocrine imbalance were explained by the sighing respiration of these patients, leading to hyperventilation.^{16,17} It has been shown, however, that the chief change in these electrocardiograms consists in a depression of the RS-T segments and these changes did not occur in our hyperventilation experiments.

The results of our investigations does not preclude the possibility that under certain conditions T-wave changes are caused by alkalosis.

Summary. The influence of hyperventilation with deep, shallow, rapid and slow breathing on the electrocardiogram

was studied. In a majority of the cases, these procedures caused a lowering of the R and of the T waves in Lead 1. These changes are similar to those obtained when the electrocardiogram is taken during maximal deep inspiration.

The alterations of the electrocardiogram are explained by positional changes of the heart. No parallelism has been found between the degree of alkalosis and the changes in the electrocardiogram.

As long as a marked increase in heart rate was avoided and the respirations were not sufficiently rapid and shallow to cause anoxia, no depression of the RS-T segment was observed following hyperventilation.

The alteration of the RS-T segments and the T-wave changes which may be observed in some women with endocrine imbalance is not due to hyperventilation.

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INJECTIONAL TREATMENT OF INTERNAL HEMORRHOIDS

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JUST prior to my entry into the Army in November, 1942, I had completed a critical evaluation of injectional therapy for uncomplicated internal hemorrhoids, but postponed its publication for obvious reasons. While in the service I had an opportunity to compare and contrast injectional therapy as practiced in civil life with hemorrhoidectomy as practiced in the Army for the same type of lesion.

MATERIAL. One hundred consecutive private* patients suffering from uncomplicated small to medium-sized internal bleeding hemorrhoids without or with spontaneously reducible prolapse were treated by submucous and interstitial injections of sclerosing solutions in a manner to be described herein. The follow-up period of study ranged from a maximum of 5 years to a minimum of 6 months; the bulk of the patients was followed for a period of about 30 months. After conclusion of treatments patients were asked to report every 3 months. This program afforded a good opportunity to detect early recurrences. The follow-up examination included a proctoscopic survey in every instance.

A study of the literature as well as personal experience led to the establishment of definite criteria before a patient was accepted for this form of treatment. In all instances it was imperative to establish the absence of active or latent inflammatory disease of the anorectocolonic tube, as well as the absence of concomitant local disease which required surgical excision. Since one of the causes of hemorrhoid formation is congestion with inflammation of the anal structures (anal crypts, anal ducts and anal glands) causing perivascular and vascular involvement, particular

attention was paid to this aspect of the problem. Whenever an inflammatory process was thought to be present, it was treated and eliminated prior to the institution of injectional therapy. Experience and the "sixth sense" were helpful in the selection of cases.

Procedure. A. Preinjectional Studies.

A complete history was obtained and a general physical examination was made. A urinalysis, a hemoglobin estimation and a serologic test for syphilis were performed. The local examination included bidigital and anoproctosigmoidoscopic examinations. Much reliance was placed on the bidigital examination which is performed by the insertion of the index finger into the anal canal and by placing the thumb on the perianal area and gently but systematically palpating the entire anal circumference in a clockwise manner. Localized areas of tenderness which may be missed on routine unidigital examination will invariably be discernible on bidigital examination. These areas of tenderness may represent localized areas of cellulitis, small hidden abscesses, acute thromboses in the deeper anal and perianal tissues or a foreign body. Upon palpating of an involved area or areas the patient usually reacts with a sudden and uncontrolled jerky motion of the body or cries out with pain. The patient remains quiet and cooperative during the examination of the uninvolved areas of the anal canal. In the presence of tender areas, especially when a deep suppuration is suspected, it has been my policy to perform a sedimentation test of the blood. Rapid sinking of the red blood cells, in the absence of other causes, usually indicates the presence of an early hidden perianal abscess.³ Roent-

* Private cases were chosen for this study because all the details of examination, treatment and follow-up have been carried out by me alone in contrast to clinic patients who are not always treated and supervised by the same surgeon.

gen-ray studies of the colon by means of a double contrast barium enema were made only when specially indicated.

B. Injectional Technique. Most of the patients under study were injected according to a somewhat modified technique described by Lloyd-Davies.¹ The sclerosing agent utilized in most cases was a 5% solution of quinine and urea hydrochloride; 5 to 10% of phenol in pure almond oil was used in a small number of patients. The first injections were made submucously above the anorectal ring about the pedicle

On occasions all high submucous injections were made in one sitting and subsequent interstitial injections were completed at biweekly or triweekly intervals. A total series of from 6 to 12 injections was required. At present quinine and urea hydrochloride is practically unobtainable. A 5% solution of sodium psylliate (sylan-sol) is now employed.

C. Postinjectional Care. The patients were informed that protrusion of the treated hemorrhoidal mass may occur upon straining, especially at defecation.

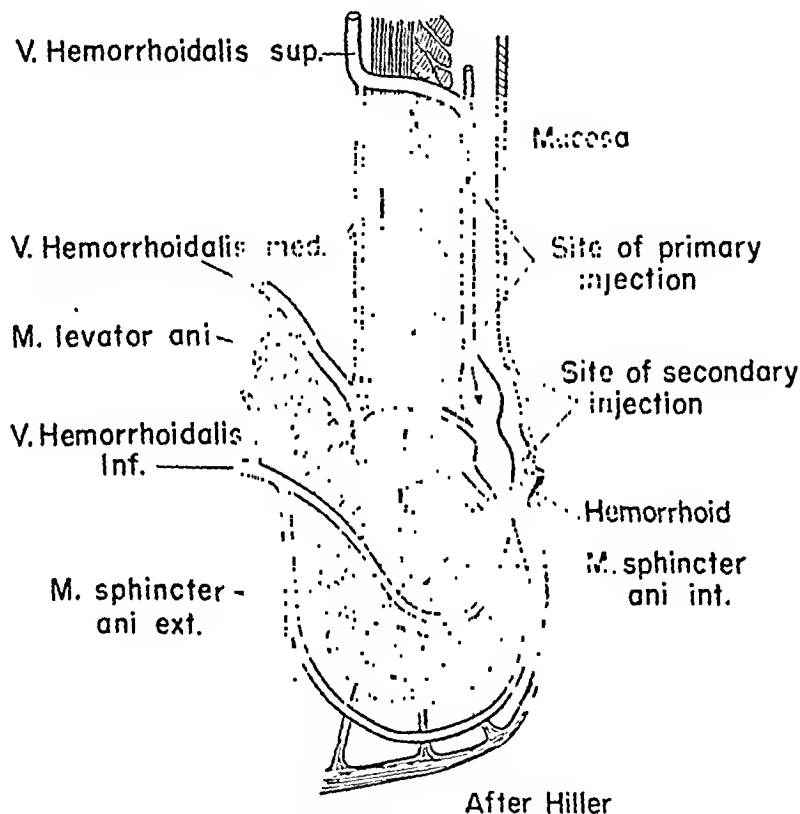


FIG. 1.—Diagram showing the primary and secondary sites of injection. Arrows indicate the reverse flow of blood in the presence of hemorrhoids (Am. J. Surg., 16, 64, 1932.)

of each hemorrhoid with a view to obliterating the hemorrhoidal vein and to fixing the mucosa at a high level in order to prevent prolapse. After all the hemorrhoids have thus been treated, subsequent injections were made into the hemorrhoidal masses at a lower level. Occasionally additional submucous injections were made between treated hemorrhoids in order to correct mild mucosal prolapse. Usually the injections were made biweekly.

Instructions were issued to avoid straining and how to combat constipation, which may be the cause of defecatory straining. The patients were asked to feel for anal protrusions and were told how to reduce such protrusions digitally and to report such occurrences promptly.

Results. Injectional therapy apparently produces a sterile inflammatory process under the mucosa and within the interstitial tissues of the hemorrhoidal plexus,

causing a chemical thrombosis of the vessels which is followed by sclerosis and finally by fibrosis. The main clinical purpose is to stop bleeding and to correct the associated descensus of the rectal mucosa. This was accomplished in every instance. About 65% of the patients remained symptom-free during a follow-up period of observation ranging from 30 months to 3 years. Reinjection was required in over 30% of the patients because of recurrence of hemorrhoids causing bleeding 9 months or more following the conclusion of the original course of treatment. Injectional therapy apparently does not produce a permanent cure. A cure depends primarily upon (1) the fate of the fibrosis produced which is a biologic unpredictability, and (2) on the elimination of the etiologic factors which had existed prior to the institution of injectional therapy. Since this method of treatment does not remove the original etiologic factors responsible for the development of hemorrhoids, recurrence can hardly be considered a failure in those instances in which the underlying cause has not been eliminated.

Complications. Seven cases of inconsequential superficial slough at the site of injection were observed in this series of patients. This complication was probably the result of leakage of the injected solution through the needle puncture, or the result of injecting too much solution. Other complications (often reported in the literature²) such as irreducible prolapse of the treated hemorrhoids into the anal canal or abscess formation, were absent in this series of patients; the absence of the former is attributed largely to the education of the patient and of the latter to the cautious preinjection examination and investigation. Parenthetically, it is my present opinion that suppuration following injectional therapy in many cases is due to an unsuspected or latent inflammatory process which was either overlooked or was impossible of correct diagnosis, rather than to the injections *per se*.

Comment. This study shows that injectional therapy is effective in a large percentage of patients suffering from small to medium-sized internal hemorrhoids without or with spontaneously reducible prolapse. This is an economic office procedure but it is neither simple nor without danger; if the limitations are understood, disappointments and complications will be avoided. The therapeutic success depends to a great extent on the patients' cooperation which can best be secured if the patients are told, in simple terms, something about their lesions and the details of the treatment and if a flat fee is charged. As in the treatment of other diseases requiring multiple injections to be carried out for a given period of time, such a financial arrangement fosters regularity of treatment, confidence, and sincerity of purpose.

To complete this investigation, I felt it desirable to compare and contrast surgical excision with injectional therapy. After treating 6 patients by operation for internal hemorrhoids that I regarded as suitable for injectional therapy, I became so convinced that small and moderate-sized internal bleeding hemorrhoids do not warrant an operative procedure that I discontinued the clinical experiment. However, renewed and ample opportunity to compare and contrast the two procedures was afforded to me while serving in the Army, as soldiers with symptomatic internal hemorrhoids (which in civil practice are considered suitable for injectional therapy) are treated by operation. This added observation and experience confirmed the conclusions of the study of the experimental series of cases in civilian practice, namely, that the majority of cases of symptomatic small or moderate-sized internal hemorrhoids do neither warrant nor require hemorrhoidectomy, with the attendant remote, but potential, risk incident to an anesthetic and a surgical procedure, and the loss of work or duty hours. This is especially true when most, if not all, of these patients can be satis-

factorily treated by the ambulatory injectional method.

Conclusions. On the basis of a study of 100 personally treated and followed patients, it appears that injectional therapy is a safe and effective ambulatory office procedure for the management of the majority of patients with small and medium-sized bleeding hemorrhoids, without or with spontaneously reducible mucosal prolapse, provided that the requirements and details of this therapy as discussed in the text are carried out.

The main purpose of this therapeutic method is to stop bleeding and to correct

the associated prolapse which can be accomplished in every instance.

In experienced hands, serious complications can be avoided. The permanence of the therapeutic results is discussed in the text.

Operation is usually not to be applied to the treatment of small or medium-sized internal hemorrhoids, but should be reserved for the treatment of large internal, or interno-external hemorrhoids, and hemorrhoids that are associated with, or complicated by, anorectal lesions that require surgical excision.

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COMPLICATIONS OF MUMPS

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NEW ORLEANS, LOUISIANA

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THE purpose of this paper is to point out the frequency and variety of complications of mumps seen on the contagious wards of a large general hospital. The material used in this study, obtained from records of Charity Hospital at New Orleans, included all patients with mumps admitted during the period from January 1, 1940, through December 31, 1944.

During this 5-year period, there were 132 males and 82 females, or a total of 214 patients with adequate clinical manifestations for analysis here. Because many patients with mild cases are not admitted to the hospital, statistics from this group may be misleading; however, most of the complications discussed in this paper developed after hospital admission.

Orchitis. Orchitis developed in 28.8% of 132 males in this series, a figure somewhat higher than that usually given in textbooks. Of the 66 who were 15 years of age or older, orchitis developed in 36; only 2 patients under 15 years of age exhibited this complication. Bilateral orchitis occurred in 6 instances; in the remaining cases the right and left testicles were involved an equal number of times. Except for the case herein reported, the course of this complication corresponded to the usual description.

Case Reports. CASE 1. A 21-year-old white man was admitted because of fever and a painful, swollen scrotum. Examination revealed a very tender left testicle enlarged to three times its normal size. There was no history of mumps recently, and the etiology of the orchitis was doubtful until 4 days after admission, when the right parotid gland became swollen, as did the mouth of Stenson's duct. Six days later swelling of the left parotid gland was noticed. Recovery was uneventful.

Meningo-encephalitis. Involvement of the central nervous system may occur at any time during the course of mumps, and this complication should always be considered in any patient with encephalitic or meningeal symptoms, particularly during epidemics of mumps. In the present series there were 3 patients with clinical and laboratory evidence of this complication. Others exhibited clinical evidence, but spinal fluid examinations were not done. The following protocols illustrate predominant encephalitic and meningeal forms, respectively.

CASE 2. A 9-year-old colored boy complained of headache and vomiting 7 days after the onset of parotitis. During the next 3 days the headaches grew worse, and he became irrational. On admission he was stuporous and lethargic but had no nuchal rigidity or other evidences of meningeal irritation. The spinal fluid was under increased pressure and contained 100 cells, 82% of which were lymphocytes. The symptoms disappeared in about 4 days.

CASE 3. A 17-year-old colored girl was admitted, complaining of mild headaches which began 9 days after onset of parotitis. For the next week the headaches became worse and were not relieved by aspirin. She was feverish during this time. On physical examination there was obvious opisthotonos with severe nuchal rigidity. Kernig's and Brudzinski's signs were positive. Examination of the spinal fluid revealed increased pressure, protein 42 mg. per 100 cc. and 600 white blood cells, of which 80% were lymphocytes. With only symptomatic measures, the condition gradually improved during the next 7 days.

Pancreatitis. The incidence and symptomatology of this complication vary widely in different epidemics. One author reported an incidence as high as 15%.¹ In the present series 3 patients with

characteristic symptoms were encountered; 2 of these had only mild manifestations, the most important being a steady, aching pain over the region of the pancreas. The third case is described because of the confusing picture it presented.

CASE 4. A 26-year-old colored man entered the hospital with bilateral swelling of the parotid glands, followed 2 days later by swelling of both testicles. Five days after onset of parotitis, while lying comfortably in bed, the patient suddenly felt severe abdominal pain just above the umbilicus, radiating toward the right side. Examination at this time disclosed an acutely ill patient groaning with pain; there was rigidity of the abdominal wall. A tentative diagnosis of ruptured peptic ulcer was made, and surgical consultation was requested. The leucocyte count was only 6,000, and serum amylase was 180 units. These considerations made the diagnosis of pancreatitis more likely than ruptured peptic ulcer. Conservative treatment was advised, and symptoms gradually subsided over a 2-day period.

Except for amenorrhea associated with 2 pregnancies, this patient has had no menstrual irregularities during the 5 years which have lapsed.

CASE 6. An 18-year-old white woman was admitted because of peri-umbilical pain, some nausea, and vomiting. During the day this pain gradually became aggravated and shifted to the right lower quadrant. There was tenderness in this area, with rebound pain over McBurney's point. The white cell count was 7,850. A diagnosis of appendicitis was made, but a normal appendix was found at operation. While the temperature remained elevated and the abdominal pain persisted during the first postoperative day, the left parotid gland became swollen, followed one day later by enlargement of the right one. Fever and abdominal tenderness persisted until the parotid swelling began subsiding. Pelvic examinations during this interval showed tenderness about the right adnexa. An interval of 2 years has elapsed since she contracted mumps, and no menstrual disturbances have occurred.

TABLE I.—INCIDENCE OF COMPLICATIONS OF MUMPS IN 214 PATIENTS AT CHARITY HOSPITAL AT NEW ORLEANS, LA. (1940-1944)

	Number	Percentage
1. Orchitis	38	17.7
2. Meningo-encephalitis	3	1.4
3. Pancreatitis	3	1.4
4. Oophoritis	2	.9
5. Myocarditis	2	.9
6. Edema of the Chest Wall	1	.4
7. Complications of Pregnancy	5	2.3
Total	54	25

The author wishes to express his appreciation to Dr. R. V. Platou, Professor of Pediatrics at Tulane Medical School, for many helpful suggestions in preparing this paper.

Oophoritis. Recognizable involvement of the ovary is a relatively rare complication as compared with orchitis. Symptoms compatible with this diagnosis were present in only 2 of the 82 females in this series.

CASE 5. A 20-year-old white woman entered the hospital complaining of swelling of the jaw and pain in the abdomen. There was no nausea or vomiting. Examination showed, in addition to the parotitis, definite tenderness over both lower abdominal quadrants. The white cell count was 4,000. Abdominal pain and tenderness subsided with disappearance of the parotid swelling.

Myocarditis. This unusual complication was not recognized clinically until recently. In 1944 Wendkos and Noll² reported a case; others have since been reported. Two examples have been studied at Charity Hospital. One of these has previously been reported and will not be reviewed here;¹ however, because of its rarity, the second one is presented briefly:

CASE 7. A 6-year-old colored boy was admitted to the pediatric ward for study of backache and low-grade fever of several months' duration. Because rheumatic fever was suspected, an electrocardiogram was made shortly after admission; it was normal,

with a rate of 90 per minute and a PR interval of 0.14 second. The leucocyte count and sedimentation rate were also normal. The hospital course was uneventful until the 16th day after admission, when the temperature became elevated, reaching a peak of 103° F. 3 days later. Examination showed swelling of both parotid glands, typical of mumps. The course of the disease was not unusual, but after 10 days of well-being, the patient had a low-grade fever and appeared less energetic. No cardiac abnormalities were detected, but an electrocardiogram at this time showed a rate of 100 per minute, a PR interval of 0.16 second, and a sharply inverted T4. These indefinite features disappeared in about 10 days, and a subsequent electrocardiogram was normal.

Swelling of the Anterior Chest Wall. Recent literature contains only a few reports of this unusual manifestation. The first case described here occurred during the period of this study; the second case was encountered more recently.

CASE 8. A 7-year-old white girl was admitted to the hospital complaining of swelling of the jaw and pain on swallowing for 24 hours. A sister had been admitted one day previously with a diagnosis of mumps. Physical examination showed bilateral enlargement of the parotid and submaxillary glands. The temperature was 103° F. The white cell count was 6,250, with 55% neutrophils and 45% lymphocytes. On the third hospital day, after the temperature had returned to normal, the swelling spread from the submaxillary region down the neck and extended over the upper anterior thoracic wall. It persisted in the latter area for 4 days, during which time swelling of the neck and submaxillary area disappeared. The white cell count at the time of maximum enlargement was 5,000, with 48% neutrophils. The patient was discharged feeling well 6 days after admission.

CASE 9. A 14-year-old colored boy was admitted to the hospital complaining of swelling of the chest. He had been well until 4 days prior to admission, when he noticed swelling of the left cheek and pain behind the ear, followed one day later by swelling of his neck. On the morning of admission the swelling extended to the chest wall, causing the patient some concern.

Seven siblings had mumps at the same time. Examination showed bilateral swelling of submaxillary glands and some enlargement of the upper part of the neck. From the level of the cricoid cartilage downward there was a very noticeable swelling of the soft tissues of the neck anteriorly, extending over the upper part of the sternum to the level of the second rib. Pressure over the involved tissue produced slight pitting, but there was no tenderness. The white cell count at this time was 7,200, with 50% neutrophils and 50% lymphocytes. Four days after admission the presternal edema had completely disappeared. Enlargement of the submaxillary glands gradually subsided during the next week. The patient was afebrile throughout the hospital course, and no other complications occurred.

Mumps During Pregnancy. A search of the literature yielded very little information on this subject; however, the occurrence of clinical mumps in 14 pregnant women out of a total of 82 females justified some consideration of both maternal and progenie aspects. Six of these patients had mumps near or at the time of an uncomplicated delivery, and each of the infants appeared normal. Three other patients had mumps and toxemia of pregnancy at the time of delivery; in each of these, a normal child was delivered, and the neonatal period was uneventful. In 1 the onset of toxemia was definitely related to the appearance of parotitis.

In 2 patients, 7 and 8 months pregnant, respectively, there was onset of labor 2 days after swelling of jaws was noticed. Although delivery and postpartal periods were normal, both babies died. The first weighed 3 pounds 11 ounces, breathed poorly, later became cyanotic, and died 1 day after birth. Autopsy revealed bilateral pulmonary atelectasis in addition to prematurity. The second infant, weighing 4 pounds 13 ounces at birth, lived for 21 days but his condition was always poor, and was characterized by intermittent cyanosis. Autopsy was not performed.

Of the 3 remaining patients, 1 had mumps during the seventh month of preg-

nancy, made an uneventful recovery and delivered at term a normal baby; 5 years later this child appeared to be normal in every respect. The second patient aborted during the fourth month of pregnancy, one week following onset of mumps. In the other patient parotitis developed during the second trimester of pregnancy, and throughout the course of the disease had abdominal pains and cramps justifying an obstetrical diagnosis of threatened abortion.

Summary. The incidence and variety of complications of mumps at Charity Hospital over a 5-year period have been discussed and a brief review of the unusual cases presented. From the data included in Table I, it can be seen that the total incidence of complications is about 25%. It seems unnecessary to emphasize that these complications almost always occur after puberty.

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FURTHER REPORT ON THE USE OF BISMUTH SODIUM TARTRATE INTRAVENOUSLY IN THE TREATMENT OF 203 ADDITIONAL PATIENTS WITH TULAREMIA

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THE 203 patients with tularemia recovered following treatment with intravenous injections of a 2% solution of bismuth sodium tartrate. The results obtained in the present series were essentially the same as those in the 61 cases reported¹¹ previously. Up to June 28, 1946, recovery has ensued in a total of 264 patients with tularemia who have been so treated.

CLINICAL OBSERVATIONS. The total series included 25 children, 18 adult Negroes and 221 white adults. The absence of any mortality is attributed solely to the fact that treatment was instituted early on a presumptive diagnosis based on the characteristic clinical syndrome and undoubted history of exposure, while awaiting laboratory confirmation. Routine laboratory studies included agglutination tests for tularemia, typhus (*Proteus vulgaris*, OX19), undulant fever, syphilis and typhoid. The serum of 90% of the patients showed positive titers for tularemia of 4+ in 1:360 dilution.

The patients' progress was marked by a routine drop of temperature to 99° F. within an average of 7 days, and all were ambulatory within 18 days. The water-soluble 2% bismuth sodium tartrate solution* was administered in 1 cc. doses daily to all adult patients regardless of sex, age or weight. The dose for children was based on an age-weight basis (an average child of 6 years is given one-half to two-thirds of the adult dose) until the daily maximal temperature remained at or below 99° F., and then every 2nd day until clinical recovery appeared certain. The total number of injections given any one patient varied from 4 to 18. Only 2 instances of gingivitis (all patients were checked constantly by the nurse for this side effect) and 1 of tularemic pneumonia

have developed among the total series of 264 patients. The history of the patient with tularemic pneumonia is presented in full in the accompanying case report.

Some of the interesting highlights of the present series of patients were: In the patient with tularemic pneumonia, the house physician thought that bismuth sodium tartrate was life-saving, especially since streptomycin was not immediately available. A Negro patient, with an ulcer on the leg which was believed to be a chancre, a 4+ Wassermann and a temperature of 103° to 104° F., was treated in the accepted manner for syphilis but to no avail. Later tularemia was diagnosed and the patient responded readily to bismuth sodium tartrate therapy. Another patient, with general adenitis, an ulcer on the leg, a leukocyte count of 7000 and a normal temperature, was taking baths at Hot Springs for supposed arthritis, and since no improvement ensued he was referred to us. We suspected tularemia on the strength of the adenitis and the ulcer, both of which promptly disappeared under bismuth treatment. Agglutination tests showed positive titers for tularemia. Because of a similar ulcer and adenitis 34 years ago in this patient's brother, we asked to see him and performed agglutination tests for tularemia; his resulting titer was 3+ in 1:240 dilution. It is believed that the agglutination test remains positive for life, although I have had opportunity to examine the serum of only a few patients 5 years after recovery from tularemia. The serum of each such patient proved positive.

That the serum probably remains positive for life was pointed out by Francis^{10a} who stated that the serum of a patient observed by Martin in 1907 showed anti-

* The solution, supplied by G. D. Searle & Co., contains 29.6 mg. of bismuth per cc.

tularensis agglutinins in 1925. This observation by Martin in 1907, who encountered several cases of the disease in human beings, was mentioned in a letter which was not unearthed until 1925.

Case Report. The patient, I. W. W., was hospitalized May 21, 1946. He had been ill since May 17. Agglutination for tularemia on admission was 4+ in 1:320 dilution. Intravenous injections of bismuth sodium tartrate (1 cc. daily) were started immediately and continued until May 29, when they were increased to 1.5 cc. and continued to June 4. In addition, 200,000 units of penicillin was given for lymphadenitis of the leg. At this time the temperature ranged from 101° to 105.4° F. A roentgenogram taken May 29 disclosed bronchopneumonia; the patient was placed in an oxygen tent until June 7. He received daily infusions of 1000 cc. of a 10% solution of glucose to which vitamin B complex was added. On June 4 (the 13th hospital day) the patient received 1 gm. of streptomycin; 24 hours later the temperature dropped to normal and after 2 gm. it remained normal except for 1 rise to 99.8° F. He received a total of 5 gm. of streptomycin. On June 14 bismuth sodium tartrate was resumed because of a slight rise in temperature, but it was discontinued on June 17 because of gingivitis. A roentgenogram taken June 18 showed residual bronchopneumonia of the right lung. The patient was discharged a few days later, and is now ambulatory, feeling well, eating well and gaining weight.

Laboratory study on May 22 showed the following: a leukocyte count of 5000; an erythrocyte count of 4,730,000; hemoglobin, 13.2 gm. (79.2%); a color index of 0.8; the sedimentation of leukocytes was 56 mm. in 1 hour by the Westergren method; the unsegmented neutrophils totaled 32, the segmented 41, the lymphocytes 23 and the monocytes 4; the Schilling index was 45+. There was no malaria. Urinalysis revealed an albumin of 2+, a trace of sugar, numerous coarse granular casts and a mixed bacterial flora. Agglutination tests for tularemia were 4+ in 1:320 dilution and typhoid and paratyphoid were cross-agglutinated. Study of the feces was negative as were the Kahn and Kolmer tests. Frequent further laboratory studies showed changes which

would normally occur in view of the patient's progress.

Discussion. Despite the favorable results that have been reported recently in a total of 13 patients following the use of streptomycin, the results obtained in my 264 patients would make it appear that bismuth sodium tartrate might be a specific for tularemia. Foshay and Pasternack¹⁰ report that in their 7 patients treated with streptomycin, fever disappeared within 2 to 25 days, the bed period varied from 4 to 28 days and buboes disappeared in 16 to 90 days. Excluding the pneumonia case, the respective figures for our 264 patients were: an average of 7 days for the temperature to drop to and remain at or below 99° F.; the bed period did not exceed 7 days and buboes cleared within an average of 21 days.

Results similar to those reported by Foshay and Pasternack have been obtained by Abel¹ in 3 patients and apparently by Foshay⁹ in 2 other patients, as he mentions in this latter article that 9 patients had been treated with streptomycin. Cohen and Lasser⁸ report an instance of tularemic pneumonia that did not respond to penicillin and the sulfonamides but in which apparent cure followed the administration of 7,062,000 units of streptomycin.

This makes a total of 13 patients with tularemia who have been treated successfully with streptomycin, but a definitely larger series will have to be had before its efficacy can be proved.

As for other therapeutic agents, in the few patients on whom I have employed penicillin no amelioration of symptoms followed its use and only after resort to bismuth sodium tartrate did recovery ensue. Indeed, it is generally accepted that penicillin has no value in the treatment of tularemia.

Bell and Kahn³ determined the therapeutic effect of the following preparations on experimental tularemia in guinea pigs: sulfanilamide, sulfadiazine, sulfamerazine, acriflavine, metaphen, iodide and bismuth, arsenic and bismuth, trivalent arsenic.

antimony, penicillin and hyperimmune equine antitularemic serum. Their results demonstrate that with the possible exception of penicillin, none of these agents, given in doses larger than would be used for human beings, showed any therapeutic advantage. Beebe⁴ reported a fatal case of tularemic pneumonia after intensive sulfadiazine and penicillin (300,000 units) therapy.

A word of caution as to the transmission of the disease may not be amiss. The term "rabbit fever," although synonymous with tularemia, should be dropped from the medical literature since tularemia is most often caused by tick bites rather than by any of the other numerous possible contacts. In our experience tularemia followed tick bites in 97% of our patients and in only 3% had it occurred after contact with rabbits or squirrels. Pullen and Stuart¹⁵ stress the importance of contacts other than the rabbit. Their list includes rabbits, ticks, squirrels, mink, raccoons, opossums, dogs, cats and rats. These other contacts, they say, are not generally appreciated. Bow and Brown⁵ state that the known contacts in 35 of 40 cases of tularemia occurring in Alberta between the years 1931 and 1944 were rabbits, ground squirrels, cats, ticks, grouse, mink, sheep, swine and skunk. In another report Bow and Brown⁶ stressed the importance of ticks as contacts by stating that: "Ticks are next in importance to rabbits as a source of infection." However, this has not been found to be true in my practice.

Francis^{10b} stressed the importance of ticks and tick bites in the transmission of the disease to man. He says in part: "Tick bite, fly bite, and contact with the wild rabbit account for 95% of human cases in the United States." The contacts given by him are wild rabbits, hares, wood ticks, dog ticks, horse flies, sheep, tree squirrels, opossums, sage hens, coyotes, deer, red fox, bull snake, quail, ground hog, muskrat, hog, skunk, cats, Montana ground squirrel, white rats and the water rat.

To this list of vectors the experimental work of Prince and McMahon¹⁴ adds 2 species of tularemia infected fleas: the rat flea, *Xenopsylla cheopis*, and the California ground squirrel flea, *Diamanus montanus*. These fleas produced tularemia in white mice under certain laboratory conditions. These authors cite the work of others who have reported the transmission of the disease, under experimental conditions, by bites of infected flies (*Stomoxys calcitrans* and *Chrysops discalis*), ticks (*Dermacentor andersoni* and *Dermacentor variabilis*), the bedbug (*Cimex lectularius*) and the mosquito (*Aedes aegypti*).

The muskrat is accused by Williams¹⁷ who reports the first case of tularemia, the ulceroglandular type, diagnosed in Alaska. This patient's illness followed the skinning of numerous muskrats. Williams states that the muskrat as a contact associated with human infections has been reported from Oregon, Idaho, Montana, New York and at Northway on the Upper Tanana River Drainage, Alaska. Bell² discusses the nature, incidence and transmission of the infection in ticks. Byfield and his associates⁷ review the literature on the transmission of tularemia to man by animals other than the rabbit (mostly ticks) and report 15 cases of their own that occurred in military personnel following tick bites. Their patients were encountered in an evacuation hospital receiving casualties from a maneuver area in Tennessee. There have been a few other recent reports^{12,13,16} on tick-borne tularemia.

Conclusion. From a comparison of the results obtained in the 264 patients with tularemia treated by the intravenous administration of bismuth sodium tartrate and the 13 so far reported in the literature who have been treated with streptomycin, it may be concluded that the bismuth treatment has the advantage in that the fever period, hospitalization period and bubo clearance time are all considerably shortened. The mortality was *nil* for our total series of patients. The efficacy of streptomycin in the treatment of tulare-

mia must await further trial, since thus far so few patients have been treated successfully. The bismuth sodium tartrate solution that we use is easily available and in contrast to streptomycin it is

inexpensive. Finally, there are fewer possibilities of toxic side effects from bismuth sodium tartrate than from streptomycin, which may at times produce permanent labyrinthine damage with vertigo.

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PROGRESS OF MEDICAL SCIENCE

PREVENTIVE MEDICINE AND EPIDEMIOLOGY

UNDER THE CHARGE OF

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FLEA VERSUS RAT CONTROL IN HUMAN PLAGUE

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THE close relationship of communicable disease and military operations has been so long recognized, so decisive in military history, and so stressed in military planning as to be accepted doctrine. An outbreak of mumps has disorganized many a training program. Epidemics of acute upper respiratory infection continue to complicate movements of troops on long journeys. Undue prevalence of even so benign a disease as scabies can interfere with preparations for marshalling an invasion. Dysentery can disrupt a campaign.

The threat of such events is an accepted if not inevitable risk in bringing large groups of men together under conditions associated with military operations. The degree of concern warranted, and the preventive measures deemed applicable, depend upon various factors. The practicability and effectiveness of available control measures are important considerations. The expected gain in health protection

or even in health maintenance must be weighed against the inhibiting effect on conduct of normal military activities. The seriousness of a given disease in respect to death and disability may be an issue. A relatively mild condition may attain importance because of the non-effectiveness it engenders.

In developing a general program of prevention, many communicable diseases afford some leeway in procedure or give opportunity for exercise of judgment based on local conditions or the particular military situation. The 5 classical, internationally quarantinable diseases constitute a group permitting little compromise.

Typhus, cholera, plague, smallpox and yellow fever enter more pertinently than ever into military calculations as modern war has become so dominantly global. The reasons are evident and diverse. In the first place, they are capable of wide distribution. Not even yellow fever is a

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strictly tropical disease, as witness the past century entrance of that infection into our northeastern seaports.³ Cholera has invaded Kentucky.⁴ Plague exists in western United States.^{11a} Other factors include the ease with which the quarantinable diseases flare into epidemic proportions, the difficulties in control they present, and their universally high case fatality. All at some time have been pandemic, a threat which becomes exaggerated in time of war.

The control of the quarantinable diseases is, of course, no problem peculiar to times of war. It merely becomes more imperative and bears an increased significance. It has always had an important relation to the maintenance of domestic health, as a matter requiring unrelenting diligence. The international quarantine service to guard our seaports against entrance of these diseases was one of the earliest health functions of the Federal government. Air traffic has added to the complexity of this obligation. The current extension of American interests to parts of the world where these diseases are endemic and periodically epidemic increases our concern. The threat of introduction into continental United States will be more frequent. Considerable parts of our population will be resident in plague areas under conditions where American agencies and American physicians must take responsibility for protection against these communicable diseases.

Plague has a special interest at this time. It is one of 3 of the quarantinable diseases which exist within our own territorial borders, recognized endemic foci of infection being present in at least 12 western states.⁸ Infection of man has been reported from 9 states,²⁴ including 3 of the Gulf Coast states, and from the Territory of Hawaii.^{7,11b} It has a decided professional interest because of newly developed methods of control offering great promise, but still lacking the experience of extended application which will determine their ultimate value.¹³

No matter how remote interest and

knowledge of plague may be, there is universal appreciation of the epidemiologic principle that the disease spreads along lines of travel. Never in the history of war has an army traveled so far or so widely as did the troops of the United States in the recently completed operations of World War II. Never before has an army been called upon to take up occupational duties in such far-flung parts of the world. No recognized plague area of the world was untouched by American interest and influence, nor unvisited by American soldiers.

The serious plague outbreaks of modern times have been in India, in Burma, and in both south and north China, with Manchuria and Inner Mongolia more or less constant endemic centers.^{6b} Plague of the Mediterranean Coast of Africa and the Atlantic Coast of West Africa^{1,14,21} has been less extensive but frequent. The consistent presence of plague on the Caribbean Coast of South America¹⁶ and along the Atlantic Coast of Brazil^{13a} is less generally appreciated. American military operations, sometimes of major importance and extent, took place in all of these regions during the war.

American troops were stationed also in numerous other areas of recognized lower risk of plague infection, but nevertheless where the disease has been known for many years; where it periodically flares into outbreaks of varying importance; and in many of which it appeared at some time during the war and during tenure of American troops. These include the Azores, certain islands of the West Indies, New Caledonia, Hawaii, and certain western states of the United States.

Not only was the amount and extent of travel by American troops greatly increased during the war, but it was potentially more hazardous travel. Compromise of established measures for international quarantine is unavoidable in time of war. Civilian public health staffs of countries at war are depleted. Necessary supplies for prevention and control of disease among civilian populations are di-

verted in considerable part to military needs. Newly developed methods are at the first disposal of the military. Port control in invaded countries was invariably taken over by the occupying enemy forces; when these areas were liberated, organized port sanitation was commonly found non-existent. Many ordinary regulations and procedures in respect to air and sea traffic were abrogated or modified because of military necessity; others were disregarded through license, ignorance, or exigency. There was a greater potential health risk in international travel during the war, and greater possibility for spread of the quarantinable diseases.

Despite these adverse features in kind and degree and despite the long residence of United States troops in plague-infected areas, not a single United States soldier contracted plague during the war,⁹ and not a single plague-infected rat was found in a United States ship. This was not because of absence of exposure to the disease, nor lack of opportunity for infection. As was anticipated, United States troops encountered plague in both endemic and epidemic degree.

The extent to which plague occurred in areas occupied by United States troops will be outlined in general terms. Continued knowledge of the current world situation was maintained through information from health authorities and medical intelligence arising through military channels. The policy was early adopted, that energetic attack on plague in civilian populations constituted the best means for protecting American troops, through elimination of the disease in the areas where soldiers were compelled to live. There were many such areas. Opportunity was thus provided army medical officers to apply new methods of control made possible by discoveries in allied fields during the war, and to revalue accepted standard procedures.

The greatest plague threat of the war came when United States troops entered north China. This was not a normal north China. The war was over, there was in-

ternal disorganization, the country was churned up by many moving populations. Millions of Japanese soldiers had to be evacuated from these areas. Comparable numbers of Japanese civilians had to be removed to their homeland. Hundreds of thousands of Chinese and Koreans were to be returned to their countries of origin from a variety of regions. The potentialities for spread of plague were greatly increased in an area favorable to its transmission and accustomed to its presence. The problem attained no greater significance during the war. Word came to military authorities in southern Korea of the closing of the Manchurian-Korean border by reason of plague to the west. The long separation of that plague endemic area under Japanese occupation had permitted relatively little knowledge of what had transpired in the immediately previous years. A field survey was therefore undertaken to determine the plague situation in north China generally, and particularly in those localities where activities relating to displaced persons and evacuation of prisoners of war would mainly be centered. In preparation for anticipated difficulties, a detailed program of control was formulated. It included the desirable features of standard methods^{19,26} and additional measures derived from a variety of experiences with plague in several parts of the world during the war.

Standard Procedures for the Control of Plague. Plague epidemics of man begin as rat epidemics. The first clinically recognized human infections are almost invariably bubonic, arising from the bite of the rat flea. Flea feces containing plague bacilli are rubbed into the minute wound resulting from the insect bite. Depending on environmental conditions, the outbreak may or may not become pneumonic. This form of plague may be a rare event or it may characterize the epidemic. The dominantly septicemic variety of plague is either an overwhelming infection, with death before progress to bubonic or pneumonic types, or a ter-

minimal event in bubonic or more commonly pneumonic infection. Plague infection sometimes comes from duties concerned with the care of patients, through discharges from buboes or from the respiratory tract. Not a few accidental infections are contracted by laboratory technicians in the course of examination of pathologic material for diagnosis, or by control workers through contact with infected rodents.

Under any circumstances, the rat occupies the center of the stage. It was, therefore, natural and logical that traditional plague control should be directed against this animal reservoir of the disease. Basic effort has, therefore, consisted in energetic trapping and poisoning of rats, elimination of their breeding places, and curtailment of their food supply.

A second general control measure is quarantine. With this disease perhaps more than any other, quarantine finds its greatest usefulness. It is liberally used. In its point of initial outbreak, plague shows a special predilection for ports, a circumstance intimately related to the density of rat populations in such areas. Strict application of international quarantine is the first consideration among quarantine measures. At times quarantine of whole provinces is indicated, sometimes of cities, or perhaps only of an area within a major concentration of population such as the native quarter. Area quarantine is a measure dating from antiquity. Finally and particularly with pneumonic plague, quarantine and observation of individual contacts is important.

The incubation period of plague is short, a circumstance which gives practicability to these procedures. Through limiting the movements of persons incubating the infection, further contact with the unexposed populations is eliminated. Furthermore, prompt treatment is assured those who become ill, although all too often that is a matter of scant individual profit because of the inordinantly high case fatality.

Specific immunization with plague vaccine is a third general preventive measure.

Plague vaccines have been improved in recent years but the protection afforded is still short-lived. Specific protection is an essential adjunct to a control program and should be practiced widely and energetically, but the results to be anticipated are less than in most diseases where such measures are available.

At least 2 sizable outbreaks of plague during the war years were of moment to American troops because of the numbers of men stationed in the areas involved or nearby. The first was in the Yunnan Valley in China, the second involved the Suez district in the Middle East.

Plague in Yunnan, China. The plague outbreak in Yunnan,^{6a} southwest China, was by no means the most important in that country during the war years. The province of Fukien was more heavily involved, with an estimated 8279 cases. The adjoining province of Chekiang had 2085 cases. Both areas lie along the China Coast above Hongkong and were happily a problem of the Japanese. The considerable outbreak in Yunnan was of importance to the American army because it lay astride the Burma Road. The Yunnan Valley had been a plague center for many years. The great epidemic of 1894 is believed to have originated there,¹⁰ ultimately spreading to most countries of the world. It was therefore no surprise that plague appeared in 1938 in this general region, in Burma, just beyond the Chinese border. Although reports are indefinite, evidence indicates that the infection smoldered there during the next 2 or 3 years. At any rate, a second small outbreak was reported in 1940 and the same year, the disease appeared on the Chinese side of the border from February to July. A serious outbreak was noted in September and October of 1943 in the Talungchuan region. By 1944 a full-fledged epidemic centered about the general region of Nantien.

Dead rats were found in Nantien in June 1944. One week later the first human infection was noted, a family of 24 being first invaded, of whom 17 contracted the

disease and 9 died. From Nantien the infection spread progressively to nearby villages. December saw a general decrease in reported cases, although plague still continued through January of 1945. Conditions were favorable for spread, in that the whole region was heavily infested with rodents and fleas.

Control measures emphasized principally a rat campaign. Epidemiologic studies arising from this experience indicated available standard measures were applied to all possible advantage permitted by local circumstances in such a region. In the latter stages of the outbreak a large proportion of the population was vaccinated. In Nantien village, 59% of patients with plague were stated to have been immunized previously. Sulfonamides were employed to some extent in treatment of the disease. The generally lower death rate in the Nantien outbreak, as compared with usual experience in this part of China—23 deaths out of a total of 102 cases—is ascribed to these 2 measures. Deaths were most common in the older age groups, among those who had not been immunized, and when treatment was inadequate.

Thus, despite traditional plague control measures under fairly favorable circumstances, the outbreak in the Yunnan Valley smouldered along for 6 years. The disease spread by extension along routes of travel northward. It would appear to have been limited more by exhaustion of susceptibles than any other factor; for example, the village of Nantien with a population of 1000 had 102 cases which, judged by usual experience in China, probably represented no more than a fraction of the actual number.

Plague in Suez. The territory lying along the Suez Canal is a plague area of long standing, though the disease had last been reported in 1932. A few scattered cases occurred in 1939 and apparently an epidemic began to build up from then on, with a few scattered infections occurring each year.²³ In November of 1943, a serious epidemic developed in the city of

Suez.²⁵ From this port city at the south end of the canal, plague spread northward, involving the town of Fayed in February and Ismalia on March 25, although the disease probably had existed before that date. Plague became epidemic in Port Said at the north end of the canal in April. In all, 1581 cases were reported in the area during the winter of 1943-44. Traditional measures of control were employed; a campaign against rats, immunization of troops stationed in the area and to an extent of civilians, and application of quarantine.

These 2 outbreaks in different parts of the world illustrate the difficulties in control of plague by traditional measures of rat control, immunization, and quarantine. That control was not very effective is demonstrated by the length of time the outbreaks persisted, and by their continued progression by extension. Part of the lack of efficiency arises from inadequacies of the measures used. Plague is spread by the rat flea and not by the rat itself, consequently an attack on the rat is at best an indirect measure. On the other hand, lack of accomplishment also arises from the fact that the measures used are often not applied to their maximum. The places where plague occurs are traditionally lacking in trained health workers. There is commonly a lack of responsibility on the part of the population and an unresponsiveness which considers plague one of the inevitable afflictions of life. Supplies and other facilities for satisfactory execution of preventive measures are commonly insufficient. Reporting of all communicable diseases is usually inadequate in the parts of the world where plague is most common, and plague follows the general rule. In China, health officers regard an increase in the number of funerals as the best index of a new epidemic. Consequently an outbreak of plague gains much headway before its existence is realized, and even then rigorous measures may be delayed, sometimes apparently because of the political inexpediency of admitting that the disease

has grown out of hand. Some of these difficulties in plague control are innate and fundamental to the situations under which plague epidemics develop. Improvement in plague control depends in large measure on development of better health organizations. Nevertheless, a simple control measure which would permit direct attack on the flea instead of indirectly against the animal host—a method which is relatively cheap and capable of being applied by workers with little training—would unquestionably be a distinct advance.

DDT in Plague Control. Dakar, and West Africa generally, have a long history of plague. The region is a recognized endemic focus of the disease, and because plague tends to occur periodically, a continuous rat control program was included in the general health program in Dakar for many years. Trapping of rats, use of SO_2 gas in rat burrows, and application of poison in sewers were measures energetically employed from 1934 to 1938. War brought a generally decreased emphasis on rat control, so that during the period 1939 to 1944 little was done. There was general agreement among local observers that the rat population of Dakar had increased appreciably. It was therefore not surprising that plague appeared on April 20, 1944,^{2a,18} and that typically the first patient was a native occupying a guard hut near the docks in the Arsenal area. Control measures were promptly instituted. Standard port quarantine was established and an active immunization program got under way, in the course of which some 137,000 natives were immunized against plague by use of the single-injection French type of vaccine.

American medical officers introduced a number of measures primarily intended to protect American troops stationed in this region.¹² The waterfront where plague first appeared was placed out of bounds. Native laborers in American military installations were decreased to a minimum. Those still employed were vaccinated and subjected to frequent physical inspection to assure freedom from fleas and to deter-

mine developing illness. Later in the outbreak, all employed natives were required to live in a compound in the military area and association with native quarters of the city was prevented. Contact between American soldiers and natives was minimized. American military authorities also for the first time introduced a new measure in the control of plague, in that all quarters occupied by United States troops were dusted with DDT powder, as were all personnel of the United States forces and all employed natives.

The municipal authorities closed all cinemas and discouraged group meetings of any kind. Travel was restricted in and out of the city. Natives were required to carry a sanitary passport showing that they had been immunized and this document was required for the drawing of rations. These measures continued until the epidemic subsided in December. Infected areas within the native quarter were completely quarantined by institution of a *cordon sanitaire* which continued in force until 10 days after the last reported case.

French health authorities had a standard measure for control of plague as it was reported in native areas. The house, yard and general premises where plague had occurred were liberally treated with cresol solution, using a fire truck for gross-spraying and the common garden sprinkler for smaller and less accessible areas. The object was to kill fleas and plague bacilli. Fumigation of the "infected" house and sometimes of adjoining houses was carried out with chlorpierin gas. The house was covered with a tarpaulin, the liquid gas poured on or under the floor and the premises held isolated for 24 hours. The general rat clean-up included adjacent houses. Sulphur dioxide was passed into rat burrows, debris was removed and rats were trapped. Immediate contacts of patients were transferred to an isolation station where their temperatures were taken twice daily. During a part of this experience sulfadiazine was administered in amounts of 20 gm. for adults and 6 gm.

for children over a 3 day period. No factual data are available, but the results of chemoprophylaxis were judged to be good from a limited experience late in the course of the outbreak. Before chemoprophylaxis was instituted, 19 contacts had become ill with plague. After its use only 1 developed the disease. The basic numbers treated were not available.

Despite these measures, plague in Dakar increased during successive weeks of early summer. Eventually, through efforts of United States military authorities, the DDT method of attack which American authorities had been using since the beginning of the epidemic in United States areas and for United States installations, was applied generally as a coöperative effort to all premises where plague had appeared. Houses were dusted with 10% DDT powder. All native residents in the area were likewise dusted.

The area selected for treatment included all territory within a radius of one block of a recognized plague focus, the equivalent of nine square blocks. Later this area was extended in an attempt to anticipate the plague frontier. It became evident, however, that the focal method of attack did not suffice, for plague continued to appear. It was the opinion of American epidemiologists that the areas treated were too limited and that success depended on universal dusting of the whole native area of Dakar, the Medina. Because of disagreement over the necessity for this measure, American authorities withdrew from general plague control activities on Sept. 8, 1945. A continued high incidence of the disease led to subsequent agreement and on October 24 a comprehensive plan to disinsectize the entire native area was undertaken. The work was completed on November 10. As a part of the plan, natives living outside the Medina were provided opportunity for disinsectization on a voluntary basis.

The native quarter was divided into 13 zones. Without notice a cordon of gendarmes was placed around a selected zone at 0500 hours. Four outlet stations

in the cordon permitted residents to pass out of the restricted area on their way to work after they were dusted, beginning at 0600 hours. The standard personnel dusting technique was employed and the working population had departed completely dusted within 1 hour. An inner-cordon was then established to isolate individual blocks of the area, and members of the dusting teams went through these areas one by one, dusting all natives who had remained at home, the outer cordon being gradually constricted until all within the prescribed area had been treated. It is estimated that 95% of the inhabitants of a selected zone were so disinsectized. Houses and premises were treated by residual spray or powder. The floor, walls and beds were heavily treated and a lesser dosage applied to the upper walls. In addition to dwellings, all public houses, cafes, restaurants, bars and cinemas were likewise treated. It is estimated that in the course of this work, during which all 13 zones were treated, a total of 125,000 natives were disinsectized with DDT powder. The general program having been completed, fixed stations were maintained in the area, where natives could come for treatment voluntarily in case of reinfestation with vermin.

A major reduction in the flea population of both natives and houses was accomplished. The extent of infestation of houses with fleas of all species, before institution of these measures was determined by first stirring up the fleas through waving the hands, and then exposing a standard piece of fly-paper for 5 minutes. Fleas collected under these conditions sometimes numbered between 200 and 300. Observations after the dusting process showed that houses remained free of fleas for several weeks, the period depending upon dosage applied, the subsequent treatment of the usual sand floors, and the amount of traffic in and out of a given house. Two weeks after completion of the program, 316 houses were visited and only 7 were found to harbor fleas. Under previous circumstances infestation would

have been essentially universal. A second survey on Dec. 8, 1944, showed 33 of 1643 houses to harbor fleas, a proportion of about 2%. It is clearly evident that the method of treatment served to diminish the flea population in remarkable degree. Complete efficiency cannot be attained by such a mass effort. Some houses are invariably missed. Of the 7 houses that had fleas after 2 weeks, the primary dusting had missed 5.

This experience unfortunately does not give a clear evaluation of results to be anticipated from this new method of plague control. The procedure was started late in the epidemic, on Oct. 14, 1944, when reported cases were declining, a seasonal expectation. Nevertheless, the last case of plague was recorded on Nov. 25, 1944, when a native was found dead. It is possible he had been infected prior to completion of the dusting campaign. In any event one accomplishment was wholly definite—the flea population in the native quarter was reduced to almost unbelievably low limits. The outbreak in Dakar was directly concerned with flea-borne transmission, for no patients with pneumonic plague was observed in the course of the outbreak.

Significance of the experiment was increased by the French attitude toward rat extinction. The opinion was held that if rats were killed in appreciable numbers by poison, and the carcasses not recovered, the fleas would leave the rats and go to man as an alternative host. This is in explanation of the standard procedure in rat campaigns in the Dakar area which required that rats be caught alive and drowned in cresol to insure destruction of fleas as well as rats. Because of this policy the number of rats caught and destroyed in Dakar during the course of the outbreak was never very great. This strengthened the presumed accomplishment arising from disinsectization.

The field studies in Dakar were subsequently corroborated by entomologic observations on the lethal action of 5%

solution of DDT in kerosene on fleas.¹⁷ When this material was sprayed on floors in concentrations of 100 mg. per square foot, the biting activity of adult fleas was inhibited in 10 minutes. The residual killing effect persisted for 21 days—10% DDT powder applied to floors had essentially the same effect as 5% DDT in kerosene.

Further observations on the control of rat fleas, *Xenopsylla cheopis*, by DDT have been reported.⁵ Flea-infested rats treated with DDT powder were not only freed of fleas, but fleas in jars that served as cages were likewise killed. Rats were captured in buildings before and after the building was dusted with DDT. The flea index was 13.9 fleas per rat before dusting; 1 month after dusting it was 0.6; and in 2 instances 0.2 and 0.5 fleas per rat 4 months after dusting.

Chemoprophylaxis of Plague. The suggestive results of chemoprophylaxis in Dakar were extended and given more precise evaluation during a small outbreak of plague in Oran in 1945. This epidemic²⁰ was part of a general increase in plague along the North African Coast that started in Ferryville in the autumn of 1944. The first patient with plague in Oran was a dock worker, who died Jan. 6, 1945, of an illness originally considered influenzal pneumonia, with onset Dec. 29, 1944. Subsequently 8 other natives contracted pneumonic plague, all being close associates of the original dock worker. Spread was by direct contact, and included 2 nurses and a priest attending patients in the hospital. Chemoprophylaxis was employed for 85 direct contacts, maintained under guard during the period of observation and treatment, and given 3 gm. of sulfathiazole daily. Only 1 became ill with plague, and this infection resulted in recovery. The favorable but inconclusive impressions about chemoprophylaxis for bubonic plague in the Dakar experience were confirmed by these satisfactory results with the more serious pneumonic plague in Oran.

Though no rodent plague was ever dem-

onstrated in the Oran outbreak, preventive measures included rodent control. The Dakar experience with DDT was used liberally. Buildings and areas were sprayed with kerosene solution of DDT. Bedding, clothing and persons of natives were treated with DDT powder. Public gatherings were prohibited and areas of infection were placed off limits to soldiers. All members of the U. S. Army were restricted to post during the acute phase of the outbreak. Rat trapping at strategic locations, with examination for plague, was instituted to determine the distribution of plague infection. Segregation of United States from native dock workers was practiced. Troops scheduled for shipment to other ports or areas were isolated for the appropriate incubation period before departure. Re-immunization of military personnel was practiced. Sulfonamide chemoprophylaxis of all inhabitants of heavily infected districts was reserved as an emergency measure. A general conclusion arising from these observations was that larger doses of sulfonamides than those employed were in all probability desirable.

Plague in Casablanca. Plague of both bubonic and septicemic types appeared in Casablanca^{2c} on July 20, 1945. As so often happens, the first case involved a French employee in a warehouse of the port area where dead rats had previously been noted. The outbreak was limited to 3 cases, 2 natives and 1 European with no cases among American soldiers stationed in the city.

Control measures instituted by American military authorities included immunization, off limits restrictions except for those recently immunized, and extensive treatment of areas and persons with DDT powder or DDT in kerosene, including warehouses, small buildings, offices, trucks and ships. Strong emphasis was placed on protective clothing. A rat campaign was started. The few cases limited to a single week speaks for the efficiency of these newly developed control measures.

A Modern Program for the Control of

Plague. The new insecticide DDT, developed in the course of the war, has brought about a readjustment of attitudes and procedures in the management of epidemics of human plague. Suggestive results achieved in Dakar were further established at Casablanca and by laboratory experiment. The need for a fundamental ecologic attitude^{15b} toward the broad problem of plague and its control remains undisturbed. The rat is still the principal reservoir of the human disease. The effectiveness of the new techniques now available serve, however, to establish the principle that attack on the flea is the desirable immediate objective with attention to the rat a long term consideration. Experience in the Oran epidemic enlarged the preliminary observations on chemoprophylaxis as a preventive measure. Results were particularly significant in that the disease was pneumonic plague. This clinical form has a characteristic high case fatality, and attempted interruption of transmission by attack on rodents or fleas is a most indirect approach.

The principles defined as a result of these experiences permit evolution of a more modern program for the control of plague. Three sets of circumstances enter into consideration in respect to the need for plague control and the selection of measures to be applied. The first involves a community with a history of previous plague infection, presumably susceptible to recurrence, but with plague currently absent. The second circumstance pertains to a situation where plague has just appeared, as evidenced by the first sporadic cases. Sound and energetic measures must be brought into play if a widespread epidemic is to be avoided. A third general situation, all too common in areas and populations where plague tends to appear, is of the disease already epidemic or existent in greatly increased proportions; the first report is of an epidemic.

PLAGUE A THREAT. Potential danger of residence in an area frequently plague-infected requires continued attention to

preventive measures and their conscientious practice, even in the absence of known current infections. This applies to all recognized endemic foci.

Vaccination. Irrespective of the practice of native populations, foreigners and military personnel entering endemic areas should be immunized against plague at least 2 weeks in advance of arrival. Initial immunization^{2b} consists of 2 subcutaneous injections of plague vaccine, at an interval of 7 to 10 days. The first dose is 0.5 cc. and the second 1 cc. of vaccine.

Protection Against Fleas. Potentiality of an outbreak of plague should be followed by continuing survey of the existing prevalence of rats and rat fleas. An appreciable incidence of fleas, corresponding to a rat-flea index above recognized critical levels, about 0.2, calls for routine protection against the human infestation through use of insecticide DDT louse powder. Weekly use of the powder on underclothing and inner surfaces of shirt and trousers insures freedom from fleas. In military practice, regular physical inspection of men and of quarters for fleas should be required at 2 week intervals.

Rodent Control. Rat surveys of areas suggestive of likely plague infection, and the necessary rat eradication programs^{2b} should be instituted by responsible health authorities. In cities, especially port cities, a systematic continuous sampling survey of rats by live trapping will be necessary. The flea index of trapped rats should be noted and rats examined for evidence of plague. Significant increases of rat population emphasize the need for more intensive effort in rodent control. Infected rats determined in the course of routine surveys are indicative of impending plague.

Medical Intelligence. Success in the control of any communicable disease depends on an effective attack in the earliest manifestations of an outbreak. This requires continued and dependable information on prevalence of the disease in the area, and in the case of plague on a system of immediate telegraphic report-

ing of primary cases. Health authorities of local civilian areas or military installations can accomplish this for their own particular area. It is essential to develop close and frank liaison with health officers of contiguous districts and in areas connected by routes of travel. In military operations, contact must be established with local civilian and military public health authorities to insure early information of plague, even in remote areas with potential opportunity for spread.

Supply. Residence in plague endemic areas requires maintenance of adequate supplies of materials essential to a control program. These include rodenticides, insecticides, flea repellents and plague vaccine. Plague does not always occur in the most accessible parts of the world. Necessary requisition of supplies should not be postponed until plague actually appears, for immediate availability may mark the difference between success in stamping out the disease in its early stages, and the development of an outspoken epidemic.

Training of Personnel. Three special groups of workers are required to carry out modern plague control. Because plague is a disease of uncommon occurrence from a world standpoint, special plague control teams should be organized and instructed in the clinical, epidemiologic,^{15a} and diagnostic features^{15c} of this disease in advance of known cases. A thorough program of attack should be conceived in advance. Special disinfecting teams are to be instructed in the use of DDT powder and residual sprays, and in measures to be used in disinfection of persons and premises. The third general need is of laboratory facilities essential to early and certain recognition of the disease. Again, the plague bacillus is not as familiar even to trained bacteriologists as are the agents of diphtheria or tuberculosis. Perfection must be attained in examination of blood, sputum and tissues, and in recognition of rats and rat fleas.

PLAGUE A REALITY. The first appearance of plague should bring into play all

measures available^{22a} to eliminate promptly the beginning centers of infection which so often progress so readily to the condition of an outspoken epidemic. The first essential is unequivocal diagnosis. This is a function of experienced epidemiologists in collaboration with laboratories. Primary attention must be directed to patients determined to have plague and to their immediate contacts and environment.

Isolation of Patients. Patients and suspected patients should be kept in separate, finely screened rooms and only authorized and instructed attendants allowed to enter. Attendants of patients with pneumonic or suspected pneumonic infection must wear hoods with goggles or plastic eye-openings, coveralls or complete gowns with trousers, and rubber gloves. All waste articles contaminated by discharges must be burned. Bedding, linens and utensils in contact with the patient should be sterilized by boiling or autoclaving. When a room is vacated the walls, floor and furniture should be disinfected by washing with 5% solution of compound cresol and the room allowed to air for 48 hours. Persons handling bodies of patients who have died of plague should observe strict aseptic precautions.

Quarantine of Contacts. Contacts and suspected contacts of patients with pneumonic plague should be disinfested, segregated and their temperatures taken every 12 hours for 7 days. Those who develop fever should be isolated regardless of the suspected cause. Close contact of segregated persons should be avoided. Inspecting personnel should wear gowns, coveralls and rubber gloves and should be dusted daily with insecticide powder.

Because of the nature of populations usually affected by bubonic plague, the difficulties in controlling their activities, and in assuring proper medical inspection, it is usually advisable that the same measures be employed with this form of the disease as with the pneumonic variety. Precautions in their management need not be as rigid, however, if the area is one in which pneumonic plague is uncommon.

In climates where transition from the bubonic to pneumonic type is likely, every precaution should be followed.

Chemoprophylaxis of contacts is strongly urged. Not less than 3 gm. of sulfadiazine should be administered each day for 7 days. This is minimal and may well be increased to the limit of clinical tolerance. Doses as high as 8 gm. per day for the first 3 days have been used for adults. Dosage for children is in proportion to age. The high death rate from plague and the rapid development of the infection require early and intensive application of the method. Vaccination of primary contacts cannot, of course, be expected to yield results because of the time required for production of specific antibodies.

Area Quarantine. Civilian communities where plague is occurring should be proscribed to outside populations until the danger is past. Traffic patrol should be established on roads leading to the infected community to enforce quarantine regulations and to insure that persons entering or leaving the infected area are disinfested with insecticide powder prior to exit or entry. Provisions for such infestation should be maintained at road blocks. Control may be made more effective by requiring possession of sanitary passports attesting to vaccination and/or to dusting within a prescribed period. Such sanitary passports can also include the name and address of persons to be visited in the infected area. Definition of the quarantine area depends on the particular epidemiologic situation. It may include only a small restricted area within a city or a district or the entire city. Small villages are treated to advantage as a unit. Within a restricted area, cinemas must be closed and group gatherings and meetings discouraged. The common tendency of inhabitants of a plague infected community to flee to the country or to neighboring villages must be curbed, forcibly if necessary. If refugees are incubating the disease or carrying infected fleas they tend to spread the disease widely.

Foreign Quarantine. Departure from plague areas should require certification that persons are free from plague infection and their clothing and equipment free from vermin. Procedures necessary to permit such assurances should be carried out within 48 hours of departure, including inspection and disinfection when indicated.

Vessels having contact with ports in plague areas should be protected against entry of rats. This may be accomplished by use of rat-free wharves, by lighterage, or by fending off from wharves a distance of at least 1 meter. Adequate rat guards must be maintained on all lines from vessels to docks or to other vessels and the policing of cargo decks and gang-planks given particular attention. At night, decks and gang-planks should be lighted brilliantly. Steps should be taken to assure that cargo taken on is free from rats. Rat trapping should be continuous on vessels having contact with plague ports, with adequate inspection and fumigation when deemed necessary by quarantine authorities at ports of entry in non-plague areas.

More than the common lip service frequently observed must be enforced under conditions of actual plague risk. This involves as primary requisites a clearly defined, practicable and widely published policy, adequate local supplies and equipment, and above all intelligent, instructed and critical supervisory personnel with adequate authority to enforce their mandates. When military operations are involved, military authority and personnel must supplement the civilian. Generalized platitudes and unkempt waterfront personnel are inadequate when real risk is involved.

Cargo liable to be or actually flea-infested should be assured free from infestation by appropriate insecticidal measures. These may include or consist in storage for adequate periods in flea- and rat-free warehouses. When long voyages are in prospect, intransit time may be taken into account in assuring freedom

from fleas when freedom from rodent exposure is assured.

With increased transportation of freight by air many of these precautions must be enforced at airfields. Fortunately, classes of persons most likely to be plague infected or flea-ridden are least likely to travel by air, though exceptions may occur, especially in military or evacuation movements. Effective practicable protection in air as well as in motor traffic demands legitimately elastic enforcement by critically intelligent personnel of applicable effective measures. An uncritical routine may be both onerous and ineffective.

Immunization. Foreign populations and all military populations in plague endemic areas will have been immunized against this disease. They should immediately receive a stimulating dose of 1 cc. of plague vaccine on report of plague in the area. If the outbreak continues this should be repeated every 4 months. Consideration should be given, depending on epidemiologic considerations, to immunizing native populations. This is a desirable part of a long range program though immediate results in decreased incidence cannot be expected. A widespread vaccination program is not the first procedure among personal protective measures. It is very definitely the protection of primary direct contacts by chemoprophylaxis.

Flea Control. The modern control of plague is based on the premise that the flea is the primary objective and that the rat suffering from the disease or harboring fleas is of secondary importance. The principle of focal disinfection applies.

It is wasteful to attempt to free the universe of fleas, and attack should center about known infected areas, the house or buildings where a plague patient has been discovered. Having described an area within a radius of about 200 yards around the infected house, all persons and infestable things within that area should be disinfested, starting peripherally and working toward the central focus of infection. This is accomplished in respect to persons by dusting every individual with-

in the area with 10% DDT powder.^{22c} Pets and domestic animals are treated the same way. Clothing, bedding and furniture within houses are likewise dusted with DDT powder. Walls, ceilings and floors of houses, with especial attention to cracks, are treated with DDT residual sprays in oil. Rat runs and rat harborages are dusted with DDT insecticide powder.

Once the original prescribed focal area has been treated and disinfested, rat trapping lines should be run radially beyond the focal zone. If plague infected rats or rats with high flea indices are discovered, disinfestation should be extended, again proceeding inward from the outermost point of suspected infection.

Depending on the degree of success attained with focal attack, the extent to which plague is present in various parts of the area, and the general trend of incidence, consideration should be given to disinfesting methodically all parts of the affected section of the city or district. This is best accomplished by defining grids or sections of the general area, establishing police cordons, and methodically treating with DDT all persons and susceptible things within the area. It is invariably wise to start with the focal method of attack. This may be enlarged either by extension of the original focal area, or on a general community basis.

Foreign residents within or adjacent to a plague infected area should be disinfested weekly with 10% DDT powder, applied by hand or power duster.

Hospitals, barracks, mess halls and store rooms of military installations and the quarters, clubs, stores and common meeting places of foreign residents, within or adjacent to a plague infected area should be kept free of fleas by use of DDT powder or residual sprays. Rat harborages should receive special attention.

Protection of Personnel Engaged in Plague Control. Personnel engaged in plague control should apply insect repellent to exposed skin in the manner prescribed for protection against mosquitoes. While repellents do not prevent fleas from

lighting, the insects nevertheless tend to leave the treated surface almost immediately and do not bite. Clothing, including socks, should be impregnated as with dimethylphthalate. All personnel should be required to wear trousers tucked into boots or leggings, and shirts with long sleeves.

Rodent Control. When human plague is discovered, the extent of the disease among the rodent population should be determined by trapping in every direction from the determined focus of infection until no additional infected animals are found. Destruction of harborages, rat-proofing and rat extermination should be carried out subsequent to focal disinfestation, by working again from the periphery towards the center of infection. All buildings and ships should be rat-proofed. Rat extermination should include trapping, the use of poison, and fumigation. Finally, attention should be given to garbage collection and disposal, to removal of trash piles and to protection of foods as measures to decrease the rat population, and thereby the flea population.

Natives Employed on Military Posts or Within Foreign Compounds. Natives from a town or village where cases of plague are occurring should not be admitted within army unit areas or foreign compounds. The number of natives employed within such areas should be reduced to a minimum, and they should be required to live on the post or within the compound. If this is impractical, they and their quarters should be disinfested and each employee examined twice daily for fever or other evidence of plague.

PLAGUE IN EPIDEMIC PROPORTIONS. Measures indicated when plague is epidemic do not differ in kind from those required in the management of the first sporadic cases. The need is for intensified effort with expanded manpower and supplies. Ordinarily the special teams designed and available for epidemiologic studies and for disinfestation are inadequate for the needs of a true epidemic. More teams must be organized. They

need not be experts, for much can be accomplished, particularly in disinfection, by quickly trained men. Given brief but intensive instruction, case finding teams can be enlisted from ordinarily available medical personnel. The training may be by the regularly constituted organizations.

Operation of Case Finding Teams. Case finding teams are employed for epidemiologic case studies of all reported instances of plague or suspected plague, with special attention to sources of infection and identification of contacts. They initiate preliminary and emergency control measures for each suspected or confirmed case of plague, including removal of the patient to hospital, and disinfection of the patient, immediate contacts, and the patient's immediate environment. The principal effort in case finding lies in organized house-to-house search for unrecognized cases within the infected community. It is to be stressed that the knowledge of civilian living habits and of the language are helpful.

Case finding teams will make use of numerous unskilled civilian personnel in the conduct of their activities. They need to assure that immunization and disinfection of these workers is practiced regularly.

The operation of isolation hospitals in the kind of communities where plague occurs often leaves much to be desired. Through uncontrolled visiting of relatives or other inadequate control, contacts can be multiplied and extension of the disease into new communities facilitated rather than hindered by an improperly managed isolation hospital. It is the duty of case finding teams to consult and aid in the provision of adequate isolation measures.

Operation of Disinfection and Rodent Control Teams. Local disinfection is a primary function of disinfection and

rodent control teams. In the area immediately surrounding cases, surveys are made of rodent and flea populations, with the subsequent obligation of flea and rat extermination in infected communities and in nearby uninfected areas. Dusting facilities in quarantine control in ports are likewise a responsibility of the disinfection teams.

Cordon Sanitaire. An emergency measure to be instituted only after careful consideration is the *cordon sanitaire*, by which areas of plague infected territory are marked off from larger relatively remote uninfected areas. It is ordinarily without benefit to attempt this measure under other than the prescribed conditions. Furthermore, a strong natural barrier between infected and uninfected areas is requisite to satisfactory protection and guarding of a *cordon sanitaire*, such as a range of mountains or a fairly impassable river.

Summary. The first consideration in control of human plague is direct attack on reported foci of infection. This involves (1) diagnosis and recognition of the disease, which is essential to establish firmly the existence of plague, (2) isolation of the patient and of the immediate contacts, proper treatment of the patient and protection of contacts by chemoprophylaxis, and (3) focal attack on the area invaded by plague, through disinfection of premises and persons with insecticide DDT.

Further definition of cases and sources of infection through case-finding and the application of area and foreign quarantine follow in order.

General measures for limiting the spread of the infection are to be established promptly. These include the practice of immunization and re-immunization, management of remote contacts, relations with native populations, measures for personal protection of foreign and military populations and rat campaigns.

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PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
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Light and Dark Adaptation of Single Visual Sense Cells. H. K. HARTLINE, M.D., and R. McDONALD, M.D. (Johnson Research Foundation and Dept. of Ophthalmology, Univ. of Penna.). Changes in sensitivity of visual sense cells in the eye of *Limulus* during dark adaptation have been followed by recording the impulses discharged in single optic nerve fibers in response to test flashes of light. Following exposure to light the number of impulses discharged in response to the test flash is less than the number elicited by this same flash when the sense cell is completely dark-adapted. Recovery of sensitivity during dark-adaptation is rapid initially and approaches the dark-adapted value asymptotically. The higher the intensity and the longer the duration of the preceding adapting exposure, the greater is the initial reduction in sensitivity of the receptor, and the slower the recovery. Recovery following prolonged illumination at low intensity is slower than recovery following a short, bright flash, even though the initial reduction in sensitivity is the same in both cases. These results can be explained qualitatively by visual cycle of photolysis and regeneration such as that proposed by Wald.

The frequency of discharge in the response to a test flash is much less affected by light and dark adaptation than is the total number of impulses. Thus it is not possible to match responses obtained under different conditions of adaptation merely by altering the intensity of the test flash until the number of impulses is equal. During light and dark adaptation, therefore, other changes must take place in the visual sense cell than simple alterations in sensitivity due to altered concentration of photosensitive substances.

Oxygen Consumption of the Cerebral Cortex During Metrazol Convulsions in Cats. P. W. DAVIES, PH.D., and ANTOINE RÉMOND, M.D. (Johnson Research Foundation, Univ. of Penna.). These experiments were performed with the aid of micro-electrodes which measure oxygen tension locally by direct electrolytic reduction of dissolved oxygen (Davies, P. W., and Brink, F.: *Rev. Sci. Instr.*, 13, 524, 1942). The cats were paralyzed with intocoestrin to prevent convulsive movements, and were given repeated doses of metrazol resulting in periodic convulsions of status epilepticus, as indicated by electrocorticograms from the experimental area.

One line of evidence regarding oxygen consumption was obtained by following oxygen tensions at the cortical surface. An extremely flexible electrode less than 75 microns in diameter allowed such measurements to be made without movement artefacts. It was found that both venous and tissue-space oxygen tensions declined just after the appearance of the extra electrical activity of a seizure, rising again during the period of extinction. The arterial oxygen tension remained constant throughout. Since cerebral blood flow increases during a seizure, these results can be interpreted only by assuming an increased cortical oxygen consumption following increased nerve cell activity.

A second line of evidence was obtained from direct measurements of local oxygen consumption. This was done by causing sudden local occlusion of the circulation of the cortex and measuring the subsequent rate of fall of oxygen tension of the occluded region. A rigid oxygen cathode mounted on a movable arm, allowing it to be pressed against the brain, served both to accomplish the occlusion and to meas-

ure oxygen tension. By repeating the process a fairly continuous record of metabolism was obtained. In this way, it was found again, that cortical oxygen consumption increases after, rather than before, the increased electrical activity. The maximum rate is about double the initial, which agrees with the findings of Schmidt, Kety and Pennes (*Am. J. Physiol.*, 143, 33, 1945), and is only reached toward the end of the seizure. During the quiet phase consumption gradually returns to normal over a period of a minute or so.

Kidney Phosphatase in Alimentary Hyperglycemia and Phlorhizin Glycosuria. A Dynamic Mechanism for Renal Threshold for Glucose. By JULIAN B. MARSH, A.B., and DAVID L. DRABKIN, A.B., M.D. (Dept. of Physiological Chemistry, School of Medicine and Grad. School of Medicine, Univ. of Penna.). The enzymatic rôle of kidney phosphatase in the reabsorption of glucose in the renal tubules was studied under the conditions of alimentary hyperglycemia and phlorhizin glycosuria. Employing the homogenization technique in a modified method for the measurement of phosphatase activity a 55 to 70% increase in the activity of kidney acid and alkaline phosphatase was found after 2 hours in rats given 1 to 3 gm. of glucose by stomach tube.

Previous *in vitro* studies of the inhibitory effect of phlorhizin on kidney acid phosphatase activity were confirmed (Beck, L. V.: *Proc. Soc. Exp. Biol. and Med.*, 49, 435, 1942). The alkaline phosphatase activity was also found to be inhibited, 0.01 M phlorhizin producing an inhibition of 40% in acid and 91% in alkaline phosphatase activity. For the first time, an effect of phlorhizin on kidney phosphatase was obtained *in vivo*. Using very concentrated homogenates of the kidneys of rats injected subcutaneously with 140 mg. per kg. of phlorhizin in oil, it was shown that the acid and alkaline phosphatase activities of these phlorhizinized rats' kidneys

were 41% lower than the activities of similar homogenates from normal controls.

Studies on some components of the phosphorylating enzyme system in the kidney were made in the alimentary hyperglycemic state. The ATP content proved to be of the same magnitude in the kidney tissue from fasted and hyperglycemic rats. Using the technique of Colowick, Welch and Cori, an inhibitory effect upon phosphorylation and oxygen consumption owing to increased dephosphorylation was demonstrated in experiments in which phosphatase activity was increased by means of the addition of a preparation of the enzyme to kidney homogenates (Colowick, S. P., Welch, M. S., and Cori, C. F.: *J. Biol. Chem.*, 133, 359, 1940).

As a consequence of these findings, it was postulated that the phenomenon of renal threshold for glucose is at least in part an expression of the limit to which kidney phosphatase can be raised.

Cerebral Blood Flow and Metabolism in Patients With Severe Diabetic Acidosis or Coma. SEYMOUR S. KETY, M.D., B. DAVID POLIS, M.S., CARL S. NADLER, M.D., and CARL F. SCHMIDT, M.D. (Dept. of Pharmacology, Univ. of Penna., and Metabolic Service, Phila. Gen. Hosp.). During the past year 13 patients admitted to the Metabolic Service of the Philadelphia General Hospital in severe diabetic acidosis or coma have been studied from the point of view of cerebral blood flow and metabolism in an effort better to define the biochemical and physiologic derangements which occur in this disease. The group consisted of 7 males and 6 females; the average age was 43. The mean for blood glucose concentration was 560 mg. %, for arterial CO₂ content 12 vol. %, for pH 7.06. Seven patients recovered and were ultimately discharged from the hospital; the remaining 6 died within 24 hours of admission. These 2 groups do not differ significantly with respect to age, pH, CO₂, glucose, blood electrolyte patterns or cerebral blood flow

on admission. The group which ultimately recovered, however, exhibited lower blood ketone concentrations, higher blood pressure, better mental status and higher cerebral oxygen consumption at the time of the initial studies. Cerebral oxygen consumption appears to have considerable prognostic value and there is evidence for a critical level of cerebral metabolic activity, values below this being incompatible with recovery.

Cerebral blood flow is not significantly different from normal and is not correlated with recovery. This argues against circulatory failure as an immediate cause of the disturbances in cerebral function. Cerebral blood flow is well correlated with arterial pH as is also respiratory minute volume. These correlations in the face of

extremely low CO_2 tensions in arterial blood speak for hydron concentration rather than CO_2 as an important mediator of these functions in this condition.

Cerebral metabolic rate (measured as cc. of O_2 utilized per 100 gm. of brain per minute) is well correlated with mental state in these patients. It is not correlated with either cerebral blood flow or arterial pH, thus indicating that cerebral depression in this condition is caused neither by decreased blood flow nor acidosis. There is a good correlation, however, between decreasing cerebral metabolism and ketosis in these patients before and after treatment. Further studies may show a causal relationship here or elucidate an even more fundamental mechanism upon which both are dependent.

BOOK REVIEWS AND NOTICES

CURARE INTOCOSTRIN. Unsigned Abstracts with Introduction by H. SIDNEY NEWCOMER, M.D., Medical Director of E. R. Squibb & Sons. Pp. 292. New York: E. R. Squibb, 1946.

THIS book aims to acquaint the medical profession with the many new and important clinical possibilities of intocostarin, a physiologically standardized curare preparation. It is a compilation from scientific contribution concerning intocostarin and other curariform drugs. The book is arranged in 2 sections: the first section is devoted to papers concerning history, pharmacology and chemistry, the second to those concerning the use of intocostarin in anesthesia; shock therapy; spasticity, rigidity and tremor; poliomyelitis; endoscopy; tetanus convulsions; and the diagnosis of myasthenia gravis. An author index and a subject index provide concise reference to the recent literature on the subject of curare. This book accomplishes its purpose in serving to facilitate the study of those interested in the pharmacology and chemistry of curare and in making available the essential knowledge thus far obtained on its therapeutic uses.

C. L.

A HISTORY OF MEDICINE. By DOUGLAS GUTHRIE, M.D., F.R.C.S. (EDIN.), F.R.-S.E. With an Introduction by SAMUEL C. HARVEY, M.D., F.A.C.S. Pp. 449; 78 plates. Philadelphia: Lippincott, 1946. Price, \$5.00.

THE Preface to Osler's Silliman Lectures delivered at Yale University in 1913 on "The Evolution of Modern Medicine" contains a quotation from a letter written by Sir William to one of the editors in which he describes these Lectures "as an aeroplane flight over the progress of medicine through the ages," a description which could very aptly be ascribed to Dr. Guthrie's charming volume. As he states in his Preface he has attempted to "construct an outline of the progress of medicine from the days of Imhotep to those of Sir William Osler. An outline does not aim at finality, and many worthy names have been omitted in order

that the story may not interest by being overweighted with details." We think he has succeeded in his aim. This book recalls to mind that of Withington, which Osler admired so much, "Medical History from the Earliest Times." Beginning with a brief yet sufficient outline of prehistoric medicine, Guthrie continues with chapters on the medicine of the Egyptians, Greeks, Romans and Arabians, and the Medieval and Renaissance periods. Scientific medicine really began with Vesalius, and went through a long labor in which it was assisted by Harvey and the microscopists von Leeuwenhoek, Swammerdam, Hooke, and the anatomists de la Boe, Ruysch, Willis, Glisson and many others. As might be expected Guthrie is particularly to be commended for his story of the development of medical science in Scotland under the Monros, Cullen, and of the continuance of their work in London by their fellow-countrymen, the Hunters. There were giants in surgery in the early 18th and 19th centuries both in Great Britain and on the Continent, particularly in France. In London, Astley Cooper, Brodie and Abernethy; in France, Larrey and Dupuytren were great surgeons, and in Paris, Laennec, Corvisart and Bichat drew pupils from all over the world.

In the middle of the century Clio Medica moved to Germany and, until the beginning of the World War I, men like Koch, Virchow, Ehrlich and others were the great leaders. In the middle of the 19th century Pasteur in France was easily the greatest medical scientist of his day, and Lister in England the foremost scientific surgeon. Guthrie devotes adequate chapters to military and naval surgery and the conquest of tropical diseases; the rise of specialism and preventive medicine, and concludes with an excellent chapter on medical journalism, bibliography and medical history. Each chapter is furnished with adequate notes and references and at the conclusion of the book there is a classified bibliography of medical history and an excellent index. There are a few errors in the book, such as making William Penn, who died in 1718, a friend and con-

temporary of Dr. John Fothergill, who was born in 1712. It was Thomas Penn who was Fothergill's contemporary and friend.

The illustrations are notable, well chosen and reproduced. Dr. Guthrie's book deserves a warm welcome from all those who are interested in the subject. Though not a work of reference, such as Garrison's or Castiglioni's, it covers the most important subjects in medical history from the earliest times to the present day in a most interesting manner, omitting little of real importance.

F. P.

PNEUMOPERITONEUM TREATMENT. By ANDREW LADISLAUS BANYAI, M.D., F.A.C.P., F.C.C.P., Associate Clinical Professor of Medicine, Marquette University Medical School, Milwaukee, Wis., Member, Editorial Board, "Diseases of the Chest," formerly Preceptor in Tuberculosis, School of Medicine, University of Wisconsin, Madison, Wis. Pp. 376; 74 ills.; 16 tables. St. Louis: C. V. Mosby, 1946. Price, \$6.50.

THE author has gathered in compact and orderly form his observations and experiences in the use of artificial pneumoperitoneum since 1931. The book includes useful information on technique and the physiologic and anatomic changes in the peritoneum during treatment. Complications such as air embolism, accidental pneumothorax, mediastinal emphysema, subcutaneous and peritoneal emphysema, pneumocele, urinary retention, cardiac decompensation and unusual digestive symptoms are discussed. The 2nd section of the book takes up specifically the treatment of tuberculous peritonitis, tuberculous enterocolitis and pulmonary tuberculosis with artificial pneumoperitoneum. The last 48 pages discuss numerous other applications of pneumoperitoneum such as treatment of tuberculous emphysema, tuberculous salpingitis, pulmonary abscess and bronchial asthma. Dr. Banyai is conservative and takes great pains to place artificial pneumoperitoneum treatment in its proper position among all measures in the treatment of tuberculosis. The text is supplemented by numerous reproductions of Roentgen ray films which are adequate to show the results obtained, although not of the highest quality. This book should be a useful addition to the library of any clinician who treats tuberculosis.

H. C.

UROLOGIC ROENTGENOLOGY. By MILEY B. WESSON. 2nd ed. Pp. 259; 258 ills. Philadelphia: Lea & Febiger, 1946. Price, \$5.50.

THIS edition of an already popular book contains a larger number of excellent illustrations. The text has been kept brief yet fairly comprehensive. The book was originally written for those learning to interpret urograms, but many of the illustrated cases will be of interest to those with wider experience.

The technique of combined urography with ureteral catheterization, described by the author, will not and should not be used by those not trained in cystoscopic work. Nor should it be used when demonstration of the physiology of the urinary system is desired.

Despite published reports of pitressin "reactions" the author continues to advocate its use in the preparation of patients for excretory urography.

These minor criticisms should in no way detract from the overall value of the book, for it remains a valuable addition to the library of the student of urography.

C. P.

PEPTIC ULCER. By I. W. HELD, M.D., F.A.C.P., Consulting Physician, Beth Israel Hospital, formerly Clinical Professor of Medicine, New York University, College of Medicine; and A. ALLEN GOLDBLOOM, M.D., F.A.C.P., Assistant Clinical Professor of Medicine, New York Medical College and Flower-Fifth Avenue Hospital. Pp. 382; 110 ills. Springfield, Ill.: C. C. Thomas, 1946. Price, \$6.50.

THIS pleasingly printed and bound volume represents a wide personal experience with peptic ulcer and its complications. Well-organized with chapters on all phases of the problem, from pathogenesis to postoperative management, the text is profusely illustrated and easy to read. Considerable attention has been given to differential as well as to pathologic and roentgenologic diagnoses. The rarer types of peptic ulceration as found in the esophagus, Meckel's diverticulum and in childhood are discussed in detail. Numerous references are given, particularly to the German literature, and on controversial subjects the authors have summarized the divergent opinions. They have omitted from their discussion on treat-

ment, however, many of the recent American reports on such subjects as vagotomy for recurrent ulcer and the early feeding regimen for gastro-intestinal bleeding. Likewise no mention is made of the spot film technique in the section on roentgenologic diagnosis or of the work on effects of hormones on gastric function. Many will disagree with the emphasis placed on recurrent appendicitis as a factor in ulcer symptomatology and gastric hemorrhage. This book may be read with profit but cannot be regarded as an all-inclusive text. J. N.

DOCTORS EAST, DOCTORS WEST. An American Physician's Life in China. By EDWARD H. HUME, M.D. Pp. 278; ills. New York: W. W. Norton, 1946. Price, \$3.00.

DR. HUME, the only American physician at the time in Bombay, accepted a call to China in 1905 "to launch a university medical school" (Yale-in-China). This book records, entertainingly, his life there "at a time when Westerners were beginning to try to understand Chinese medical thought, and when China was beginning to recognize the need of the western approach to scientific medicine." The narrative of the author's life at Changsha gives a good picture of the modern medical missionary's work in his effort to build cultural bridges between nations of widely different histories and points of view. The author eventually retired from the Yale School, so as to turn over leadership to Chinese administrators; but, returning on a visit years later, he found "a good harvest." The famous treks to Kweiyang and 6 years later to Chungking are described in a short epilogue. E. K.

STROPHANTHIN. Clinical and Experimental Experiences of the Past 25 Years. By BRUNO KRISCH, M.D., formerly Professor on the Medical Faculty of Cologne University (Germany). Pp. 158; 24 figs. New York: Brooklyn Medical Press, 1944. Price, \$4.00.

This monograph was written for the express purpose of acquainting American physicians with the continental attitude toward strophanthin therapy in the hope of influencing them to use intravenous strophanthin in place of digitalis. Cardiologists and other internists will find in this book a

review of the literature, chiefly German, and a 29 page bibliography dealing with the pharmacology and clinical usage of the cardiac glucosides. American physicians have long been aware of the fact that intravenous strophanthin produces its effects much more rapidly than do digitalis preparations taken orally, and that consequently strophanthin is to be preferred in emergency cases of severe congestive heart failure. American physicians have long believed that oral medication, when effective, is far superior to parenteral injections for the treatment of chronic diseases. Some physicians consequently will be annoyed by the author's insistence upon the superior virtues of strophanthin, especially since no new or noteworthy experimental evidence is presented.

It is true that powdered digitalis is not completely absorbed from the gastro-intestinal tract. Ideally, however, digitalis is not given in fixed doses but in amounts which produce certain definite effects upon the patient. One hesitates to recommend routine intravenous therapy, with strophanthin, digitalis or any other drug unless all other routes have been tried unsuccessfully.

Cardiologists will be interested in many portions of this monograph, especially those reviewing foreign literature not widely quoted in this country. J. C., Jr.

DISORDERS OF THE BLOOD. By SIR LIONEL E. H. WHITBY, Regius Professor of Physics in the University of Cambridge, and C. J. C. BRITTON, Assistant Pathologist in the Bland-Sutton Institute of Pathology, Middlesex Hospital. 5th ed. Pp. 665; 71 ills. and 15 plates. Philadelphia: Blakiston, 1946. Price, \$10.00.

This edition brings the literature up to early 1945. As in previous editions, it is a well-written and clearly worded textbook for students of hematology. Since the first edition in 1935, an outstanding feature has been the addition of a summary at the end of each chapter. The following subjects have been revised since 1942: origin and development of blood cells, hemolytic anemias, anemias of infancy and childhood, hemagglutination, and blood transfusion and technique. Other subjects have been brought up to date, but apparently the book went to press before the advent of folic acid and

there is no mention of the work of Winsor and Bureh on siekle eell anemia. There is a laudatory attempt to simplify and clarify the nomenclature but it continues to be somewhat confusing—a fault of the science, not of the authors. The authors continue to emphasize that changes in the blood are most often secondary to disease which is primary in systems other than hemopoietic.

W. W.

THE ENDEAVOR OF JEAN FERNEL. With a List of the Editions of His Writings. By SIR CHARLES SHERRINGTON, O.M. Pp. 223; 27 ills. Cambridge: University Press, 1946. Price, \$3.50.

THIS book, which had its origin in a Vicary Lecture given by its distinguished author, deals with the outstanding reform of medicine of the 16th century accomplished by the most learned physician of his time, "one of the relatively few who as they enter advanced years grow more modern." The same statement might be made about the author of this book, who has brought to it a freshness of material, point of view and diction that might well be emulated by younger writers.

Fernel's *De Naturale Parte Medicinæ* (1542) is named by Sherrington as the first separate treatise on physiology composed in 13 centuries, *i. e.*, since Galen's *De Usu Partium*. Written, however, 80 years before Harvey's discovery of the circulation of the blood, and without benefit of chemistry or microscope, it treats of such matters as the Elements, Temperaments, Humours, and so on; and, as Fernel himself observes, "in passing from anatomy to physiology . . . we pass from what we can see and feel to what is known only by meditation." In his late fifties, while conducting a huge practice, Fernel composed *Medicina* (1554) (published also posthumously, 1567, as *Universa Medicina*). This is part of what was a never-to-be-completed system of medicine and consists of the *De Naturali* (here called Physiology), *Pathologia*, and *Therapeutica*. The Pathology, Fernel's best known book, has been highly and deservedly praised. Various printed portraits of Fernel are discussed in the text and in Note XI; his full-length portrait on the title page of the 1657 Elzevir Celsus might well have been included.

The list of editions of Fernel's writings and the biographic notices, which include a

translation from the Latin of Planey's Life, complete this admirable production, which offers in unusually pleasant form an entertaining picture of 16th century French science as well as a sympathetic tribute from an old admirer to a great physician and "modern man."

E. K.

THE MODERN TREATMENT OF DIABETES MELLITUS. By WILLIAM S. COLLENS, M.D., Chief of the Diabetic Clinic and Clinic for Peripheral Vascular Diseases and Associate Visiting Physician, Israel Zion Hospital, Brooklyn, etc.; and LOUIS C. BOAS, M.D., Assistant in the Diabetic Clinic and Clinic for Peripheral Vascular Diseases, Israel Zion Hospital, etc. Pp. 514; 193 figs. Springfield, Ill.: C. C. Thomas, 1946. Price, \$8.50.

DIABETES. By HENRY J. JOHN, M.D., F.A.C.P., Lt. Col., M.C. With a Foreword by Dr. WILLIAM S. MIDDLETON. Pp. 300; 74 figs. St. Louis: C. V. Mosby, 1946. Price, \$3.25.

BOTH monographs aim to guide the physician in the management of diabetes mellitus. Differences in procedure are apparent. As examples: the usefulness of postprandial blood sugars is overlooked by Drs. Collens and Boas but is emphasized by Dr. John. The former employ glycosuria, and particularly the quantitative urinary excretion of glucose, as a basic guide to treatment. The latter discusses quantitative glycosuria adequately but so briefly that it is obscured by his emphasis on the blood sugar in the adjustment of treatments. There are, of course, numerous items in both volumes which will evoke marginal pencilling by some readers; but these details should not obscure the fact that both books are satisfactory guides to the diagnosis and treatment of diabetes. In both, much of the language is that which the physician will use to instruct patients and both contain the usual diet lists, tables of body weight, etc.

In the monograph by Drs. Collens and Boas, the use of the glucose equivalent of insulin as a means of estimating the dose of insulin is adequately counteracted by their detailed directions for the follow-up observation of patients. Their series of chapters in which the treatment is related to the severity of diabetes and the type of patient

comprises one of the best presentations of practical management that has been made. The chapter on juvenile diabetes is good. The chapters on the complications of diabetes are concerned primarily with the influence of these complications on treatment and are not sources of statistical information. The chapters on peripheral arteriosclerosis present a practical summary of the methods of diagnosis and treatment used in today's vascular clinics. Finally the headings, outline and format are such that they should make this volume convenient for rapid reference.

In Dr. John's manual, the hypothesis that hyperglycemia from any cause may produce injury of the islands of Langerhans is accepted as the basis for the accurate control of diabetes by means of blood sugar determinations. There are no directions for the technique of insulin administration, which physicians know anyhow. The outline format is lacking. The text covers most of the problems of diabetes which confront physicians and supplies concise answers from the author's large experience. The charts and case reports provide a compendium of contributions. The chapter on diabetes in children is especially good, and the collection of "do's and don'ts" condenses some of the wisdom, aphorism and enthusiasm which permeate this book.

In summary, both of these monographs may be recommended. The differences in style, arrangement and viewpoint supply physicians with a choice of counsel for a single purpose, namely, good care of the diabetic.

F. L.

SKIN DISEASES, NUTRITION AND METABOLISM. By ERICH URBACH (collab. EDWARD B. LEWINN), Associate in Dermatology, University of Pennsylvania. Pp. 597; 266 ills.; 112 tables. New York: Grune & Stratton, 1946. Price, \$10.00.

THE importance of food in maintaining a balance of well-being and the use of diets to correct disease are ancient but sound conceptions. This rationale and elaboration have developed through extensive research in the physiology and chemistry of metabolism, with a literature now voluminous. Urbach has carefully catalogued the progress to date and together with his own investigations has produced a manual on the effect of food on the body in health and disease. While the main thesis is concerned with the effects on the skin, the volume holds much of interest to the internist, the allergist, the dietitian and the physiologist. The sections on nutritional causes and nutritional therapy of skin diseases are compact but complete and will be greatly welcomed by anyone who has had to deal with such refractory conditions as the various forms of eczema, the acnes, urticaria and the increased number of recognizable vitamin deficiencies. In addition, there are sections on the influence of nutrition on the physiology of the skin, diet in metabolism, food allergies and the relationship of internal disease and the skin. The inclusion of a variety of tables, and practical illustrative diets, adds greatly. The illustrations are well chosen, and the entire format is excellent. An index of subjects and index of authors are included.

R. G.

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

APRIL, 1947

ORIGINAL ARTICLES

CLINICAL FEATURES OF PATENT DUCTUS ARTERIOSUS WITH SPECIAL REFERENCE TO CARDIAC MURMURS

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Now that certain types of congenital heart disease may be treated successfully by surgery, accurate diagnosis is no longer a purely academic or intellectual endeavor. Until a few years ago many physicians were satisfied if they could establish the fact that a given heart was diseased or abnormal. A smaller number would succeed in deciding that a cardiac abnormality, when present, was congenital, but only a few felt competent to make an accurate anatomic diagnosis of the abnormality. To be sure, with increasing interest and largely through the stimulus of painstaking work of the late Maude Abbott, knowledge concerning congenital heart disease was becoming more general and more definitive during the past 2 decades. Until the splendid report of Gross and Hubbard,⁷ of the surgical treatment of patent ductus arteriosus, it remained a matter of no great consequence whether the exact anatomic lesion could be recognized, when congenital heart disease was present. Therapy was very limited, consisting mainly of hygiene and of symptomatic procedures, the occasional use of phlebotomy and oxygen, and combating or preventing infections. With the introduction of surgical treatment,

the situation has entirely changed. Already many cases of patent ductus arteriosus have been cured,^{7,8} patients with tetralogy of Fallot have been helped,^{1,2} coarctation of the aorta has been relieved by operative methods,⁵ and finally constriction of the trachea from congenital vascular ring or right aortic arch has been treated successfully.⁶ It is therefore necessary for physicians to become more familiar with the means of accurate diagnosis of congenital heart disease.

Inasmuch as simple bedside findings will always remain the bulwark of clinical diagnosis, it seemed appropriate to review a group of well-authenticated cases of patent ductus arteriosus and analyze some of the features they presented, particularly those obtained by auscultation. It is clear, that in the great majority of instances, the finding that initiates any consideration on the part of the physician of the possibility of patent ductus arteriosus will be the detection of a cardiac murmur. It is well known that the classical "machinery murmur" in the pulmonary area is fairly characteristic of patent ductus arteriosus. It has become quite evident, however, that with increasing experience the murmur is by no means

always characteristic and often has no machinery quality. It is now necessary to recognize cases that display atypical murmurs and to become familiar with the general range of the loudness and the peculiarity of the murmurs. One might ask whether patent ductus arteriosus may ever be present without any murmurs at all, or with only a systolic component.

that 11 were of Grade 3 intensity, and 1 was even called Grade 2—. This means that many cases showed what ordinarily is designated as a moderate systolic murmur and that rarely only a slight murmur was present. In 21 instances the intensity of the diastolic component was carefully noted preoperatively and the average intensity was found to be Grade 3.1. In

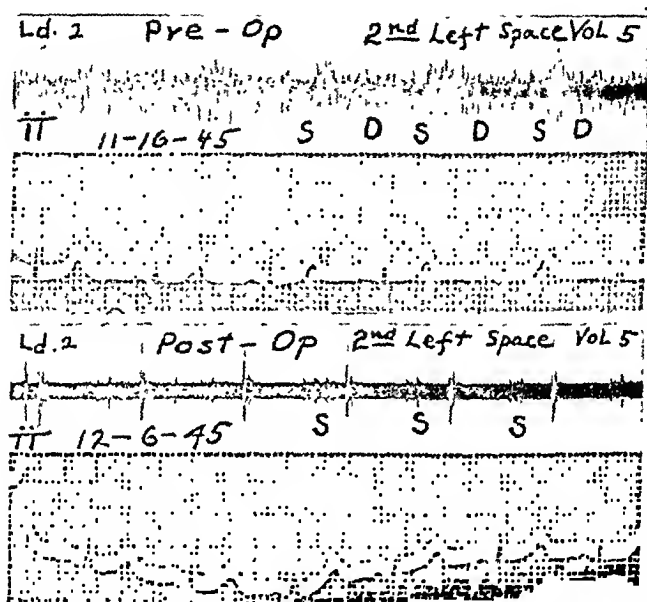


FIG. 1.—Phonocardiogram (pulmonary area) and electrocardiogram (Lead 2), before and after section of patent ductus. Note continuous murmur (above) with accentuation at end of systole (S) and beginning of diastole (D). Clinically it was of Grade 6 intensity. After operation only a faint systolic murmur (S) remains.

MURMURS. For this purpose 37 cases of patent ductus arteriosus, in which the diagnosis was confirmed at operation by Dr. R. E. Gross, were analyzed. All but 1 of these were over 12 years old, the age ranging from 7 to 47 years, the average being 24 years. Our first interest was the intensity of the murmur. The loudness was indicated by gradations 1 to 6, according to the suggestion reported in an earlier publication.¹⁰ In 25 instances in which accurate estimation of the intensity of the murmur by a competent observer was made preoperatively, the average intensity of the systolic component was found to be 4. It is of considerable interest

no instance was the diastolic component louder than the systolic, occasionally it was of the same intensity but generally it was fainter by 1 or more gradations. A peculiarity commonly observed was that the murmur appeared to become louder during the latter part of systole, enveloping the second heart sound, and continuing with decreasing intensity during diastole* (Fig. 1). In 5 cases the diastolic murmur was faint enough to be called Grade 2, and in 1 instance it was only Grade 1 (Fig. 2). In fact, the diastolic murmur in this latter case was so faint that it could be detected only after prolonged and undisturbed auscultation.

* Dr. John P. Hubbard called our attention to this peculiarity several years ago.

Although there was no instance in this series in which no murmur at all could be heard, rare cases of this type have been reported⁹ (Case 3). In another instance the murmur was found to disappear during the last month before death.⁴

The murmur was generally loudest in the so-called pulmonary area (second left interspace) but occasionally had its maximum intensity in the first or third left interspace. When it was very loud it was widely distributed, so that it could be

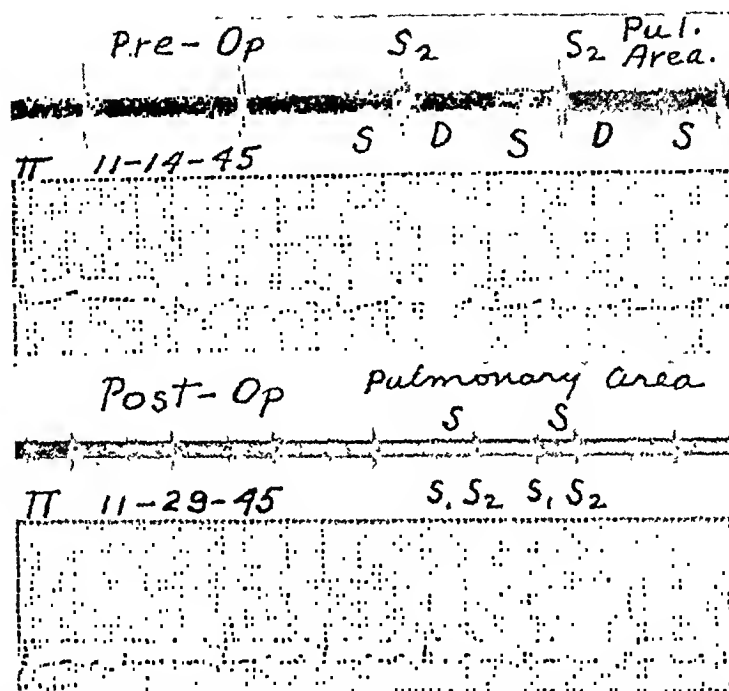


FIG. 2.—Clinically the systolic murmur was Grade 2 and the diastolic Grade 1 in intensity preoperatively and only Grade 1 systolic and no diastolic postoperatively. Note that the phonocardiograms show faint murmur. (S = systole, D = diastole, S₁ = first sound, S₂ = second sound.)

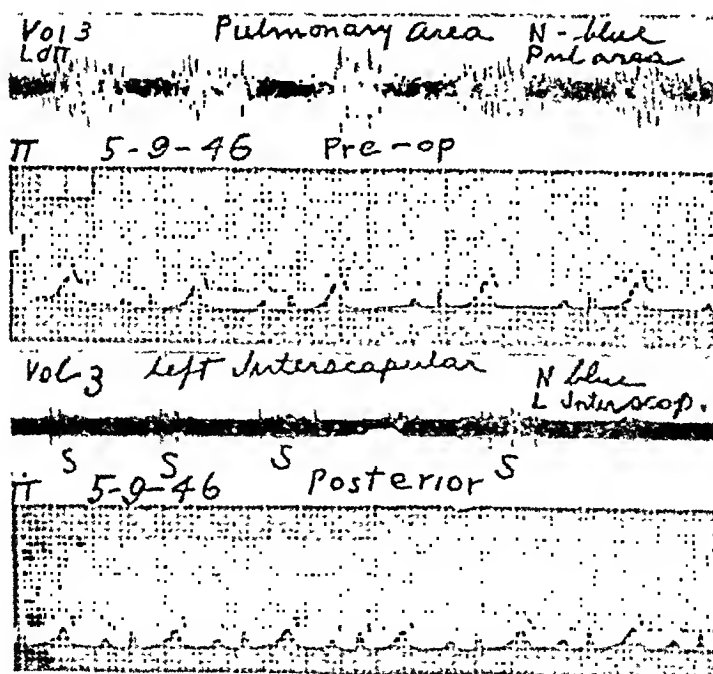


FIG. 3.—Note loud murmur in pulmonary area (Grade 3) is crescendo and diminuendo "around" the second heart sound. Murmur, though faint, can be well heard in the left interscapular region.

heard throughout the back of the chest and even at times down the arm, to the olecranon process of the elbow (Fig. 3). It is clear, therefore, that its detection in the back was merely a reflection of its intensity and did not indicate a concomitant coarctation of the aorta. Attention is called to this observation because the presence of a systolic murmur in the interscapular region has at times been regarded as evidence of coarctation of the aorta. In a rather extensive study of cardiac murmurs it has become apparent that any loud murmur (Grades 5 and 6) can be

systolic murmur was present which generally was of Grade 2 intensity, but occasionally fainter or louder (Grade 1 or Grade 3 to 4). It is of interest that in some patients the continuous systolic and diastolic murmur (though fainter) was also present at the apex, and in 4 cases a definite mid-diastolic murmur was audible, quite unlike the diastolic murmur heard in the pulmonic area and resembling a murmur of mitral stenosis. This murmur may very likely be due to the rapid inflow of blood from auricle to ventricle in early diastole.

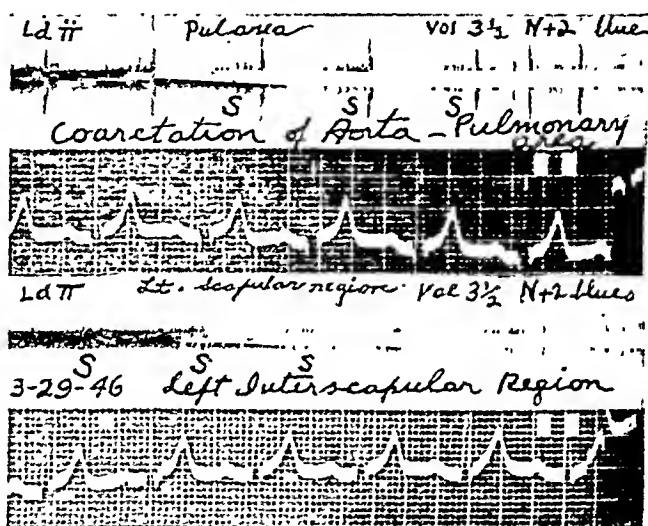


FIG. 4.—Note that in coarctation of the aorta the systolic murmur (S) is only a little louder in the front of the chest than in the back. Contrast this with Figure 3.

heard clearly in the back and that the characteristic of coarctation of the aorta is the fact that the murmur is almost as loud in the back as it is in the front of the chest (Fig. 4). The reason for this is obvious, for in the latter condition the origin of the murmur is in the arch of the aorta, which is deep in the chest, almost as near to the back as to the front.

Apical systolic murmurs were always present in these cases. It is difficult to know whether these apical systolic murmurs had an origin other than the patent ductus arteriosus, for in most cases the basal murmurs were loud enough to be transmitted to the apex. In all, an apical

After a successful operation one would expect the murmurs due to patent ductus arteriosus to disappear. Although this is commonly the result, it is by no means invariable. In the majority of instances no murmurs were present several days after the operation. It is not possible to examine many cases satisfactorily until a week or so has elapsed because of the surgical dressings covering the chest. In a few, postoperative pericarditis produced a to-and-fro pericardial friction rub which somewhat imitated the preoperative to-and-fro murmur of patent ductus arteriosus. In others a slight systolic murmur persisted in the pulmonary area for a few

days and then disappeared in about 2 weeks. During 1938 and 1939 when the duct was ligated rather than divided, there were isolated cases of recanalization with consequent reappearance of the continuous murmur. When this occurred, the murmur was less loud than the original one. There is also an instance in which a systolic and diastolic murmur persisted along the left upper sternal border. This occurred in a case of subacute bacterial endocarditis in which vegetations were found on the aortic valve

functional basal systolic murmurs. It is apparent that the persistence of a slight systolic murmur is not to be regarded as evidence of inefficacy of the operation. The persistence of a basal systolic and diastolic murmur may be interpreted in 1 of several ways: namely, recanalization of the duct, the presence of bacterial endocarditis of the aortic valve or an additional anatomic lesion such as coarctation of the aorta or some other congenital abnormality. It is of interest that a diastolic murmur did not persist in any case in this

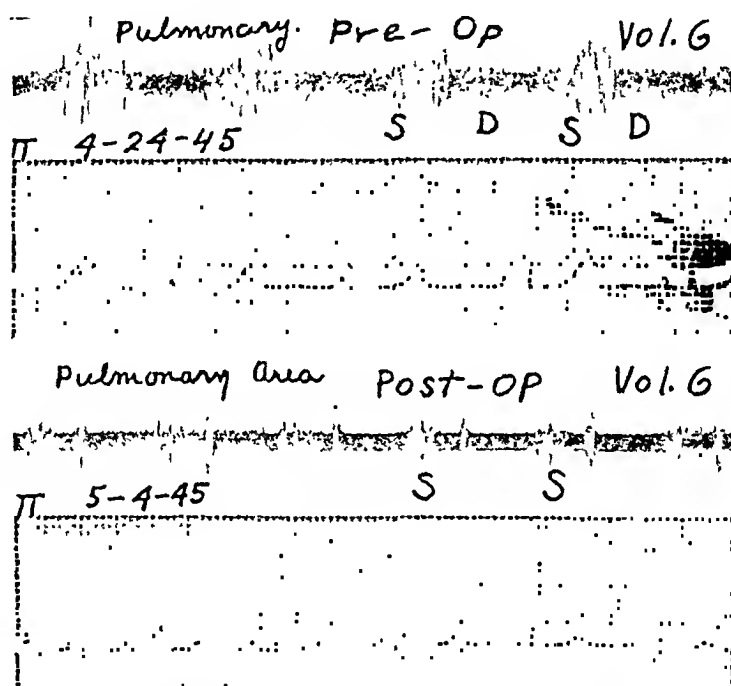


FIG. 5.—Typical case of patent ductus before and after successful operation, showing persistence of a Grade 2 pulmonary systolic murmur.

though the ductus had been ligated successfully. The most significant observation in the postoperative study was the fact that the slight pulmonic systolic murmur (Grades 1 and 2) may persist for a considerable time after successful division of the ductus (Fig. 5). Although such murmurs may disappear within a week or 2, they also may persist as long as 15 months. Such basal systolic murmurs may possibly be explained on the basis of continued dilatation of the pulmonary artery or may have the same debatable significance ascribed to other inconsequential or

series after successful division of the duct except for the occasional instance of bacterial endocarditis involving the aortic valve.

THRILLS. A definite palpable systolic thrill was present in 21 of the 37 cases. This was maximum in the second and occasionally in the first left interspace. It was always systolic in time but occasionally continued well into diastole. In a few instances, especially in thin-chested individuals, where the murmur was very loud, the thrill was palpable over most

of the precordium, and even extended above the clavicle.

BLOOD PRESSURE. A review of the blood pressure readings before and after operation confirmed what is quite well known, namely, the pulse pressure is increased in patent ductus arteriosus, and

The range of the preoperative systolic levels was from 90 mm. to 172 mm. and the diastolic from 0 to 82 mm. The corresponding postoperative range was from 100 mm. to 170 mm. systolic and 50 to 84 mm. diastolic. It is of interest that the average systolic pressure was not

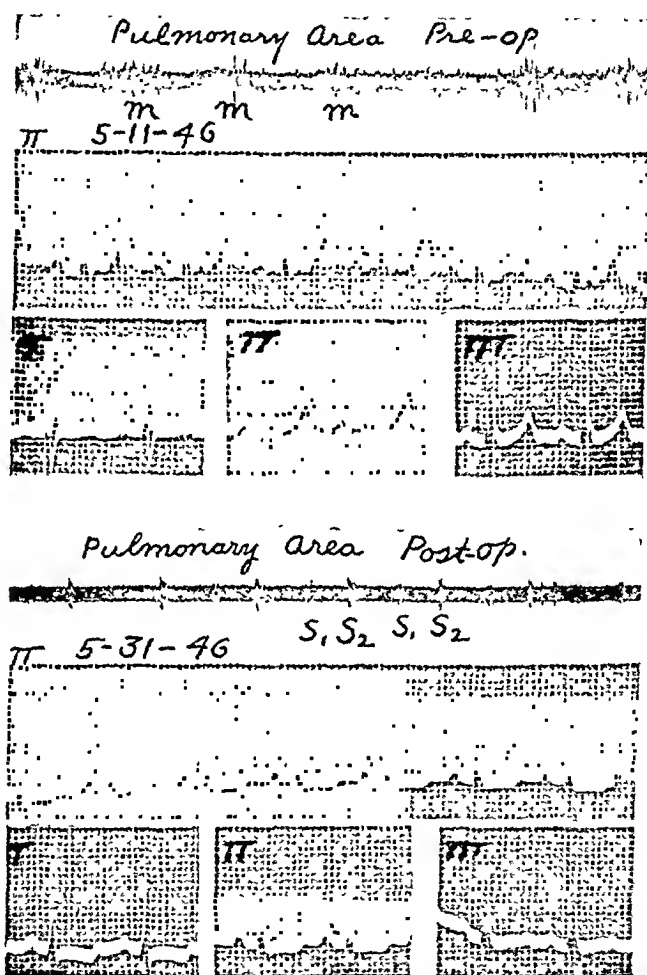


FIG. 6.—Exceptional case showing right axis deviation in the limb leads before operation and normal axis after operation. The continuous murmur disappeared.

the levels return to normal after treatment. The average preoperative reading in this series was systolic pressure 122.5 mm. Hg and diastolic 57.3 mm. Hg and the corresponding postoperative readings were 124 mm. and 78.5 mm. The pulse pressure, therefore, decreased from an average of 65.2 mm. to 45.5 mm. Hg.

altered by the operation, but the diastolic rose 20 mm. Hg. Although low diastolic pressures are characteristic of this condition there were exceptional instances in which the diastolic pressure was as high as 75 mm. and even 82 mm., when the systolic level was not over 110 mm. Hg

ELECTROCARDIOGRAMS. There were 34 cases in which preoperative electrocardiograms were available for study. The most important observation was that right axis deviation was found in only 1 instance (Fig. 6). Four showed left axis deviation, the others had a normal electrical axis. Sinus arrhythmia was present in 9, premature ventricular beats in 3, premature auricular beats in 2, intraventricular block occurred in 2 and a short P-R interval measuring 0.12 second with a QRS of 0.08 second in 1 case. There were 2 in which the ventricular complexes were decidedly abnormal, with inversion of the T waves in Lead 1 and Lead 2 not due to digitalis. The only electrocardiogram changes that took place postoperatively were those that could be ascribed to an associated pericarditis and accumulation of pericardial fluid that may follow the operation. Some developed a lowering or flattening of the T waves in Lead 1 and Lead 2 and in a few instances the T waves became slightly inverted. In several cases tracings taken some months later showed complexes tending to return to a preoperative configuration.

SYMPTOMS. The presence or absence of symptoms and the type of complaints among these cases were studied. Despite the fact that there was no evidence of right to left shunt or any other congenital abnormality apart from patent ductus arteriosus in any of these cases, 3 were said to have been a "blue baby" at birth. No significant limitation of physical activity was present in 31 of the 36 cases. The other 5 had slight to moderate restriction in activity because of varying symptoms such as breathlessness, fatigability and palpitation. Breathlessness on effort of a slight to a moderate degree occurred in 14 cases, 2 of which also complained of orthopnea and an additional one had paroxysmal nocturnal dyspnea. For the most part, when shortness of breath was a complaint it consisted of a feeling of breathlessness on running, playing or climbing stairs. In some cases these symptoms developed only in the last

months or year before operation. Pain in the precordium was quite common, occurring in 12 patients. This did not have the character of anginal pain, generally was localized in the left breast or apical region and was either of a stabbing momentary nature or consisted of a mild steady ache. It was not constricting or sternal in type. Palpitation was common in these patients, occurring in 16 instances. Fainting spells were noted in 2 and faint cyanosis in 3 of this series. A past history of rheumatic fever was striking by its absence in this group, though 3 had a past history of nosebleeds and 1 of growing pains.

An attempt was made to correlate the diameter of the duct as estimated by the surgeon with the loudness of the systolic component of the murmur. The cases were divided into 2 groups, those in which the systolic murmur was of Grade 4, 5 and 6 intensity and the remainder of Grade 2 or 3 intensity. The average diameter of the former was 11.6 mm. and of the latter 9 mm. There was enough overlapping of the 2 groups, however, to make it impossible to predict the size of the patency by the intensity of the murmur. As an illustration of this difficulty it was found that in 1 case, with a Grade 5 systolic murmur, the diameter of the duct was 6.5 mm., while in 2 other instances with Grade 3 murmurs the diameter was 15 mm. It is obvious that many factors come into play such as thickness of the chest wall, hyperactivity of the heart beat and differences in pressure in the aorta and pulmonary artery. Possibly the length of the duct apart from its width may affect the loudness of the murmur.

Comment. The development of surgical methods of treatment for various types of congenital heart disease necessitates accurate anatomic diagnosis. The general physician, who will ordinarily be the starting point in any diagnostic investigation, will have to become more alive to the importance of hitherto immaterial abnormal findings. The detection of cyanosis and clubbing of the fingers is generally easy and obvious. The finding

of cardiac enlargement is often difficult and only to be established accurately by Roentgen ray examination. For that reason it will be overlooked frequently. The presence of cardiac murmurs, however, can be determined quickly by any practitioner, even if the interpretation may be difficult. For this reason, an analysis of 37 authenticated cases of patent ductus arteriosus was made to determine some of the characteristics of the murmurs present.

It can be said that all cases had murmurs, best heard in the pulmonary areas. Generally the systolic components were moderately loud or quite loud (Grades 3 to 6). The diastolic element was about

inhalation of 100% oxygen. This latter test proved that the decreased arterial saturation was not due to a right to left shunt of venous blood into the arterial system, as that would not have been influenced by inhalation of 100% oxygen. It must have been due to changes in the diffusion of oxygen in the lungs, similar to that observed in emphysema. This case showed marked right axis deviation in the electrocardiograms (Fig. 7). It should be emphasized that occasionally the diastolic component of the murmur in the pulmonary area is so faint that it can easily be overlooked (Fig. 2).

Isolated cases of authenticated patent ductus have been reported in which no

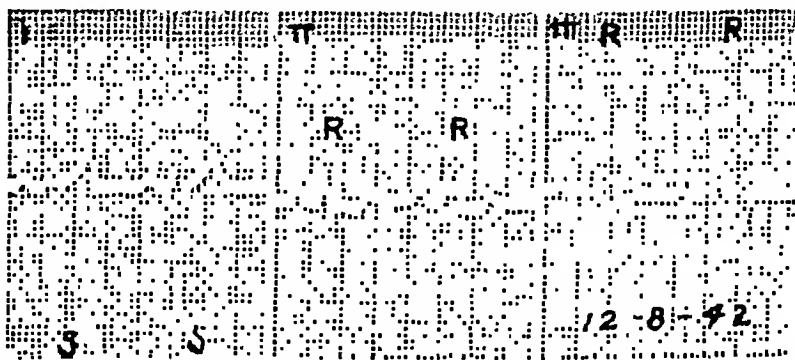


FIG. 7.—Rare case of patent ductus with marked right axis deviation. S and R indicate depth and height of the respective waves. Autopsy showed marked pulmonary arterial disease in addition to patent ductus. Patient was 37 years old.

1 gradation fainter, though in this series every one had some diastolic element. There is reason to believe that rare cases of patent ductus exist in which no murmurs or at least no diastolic murmurs may be audible. One case, not included in this series, has been studied having only a systolic murmur in which, though a significant patent ductus was present, the pulmonary arteries were so diffusely involved and the pulmonary arterial pressure so elevated that there was every reason to believe little, if any, flow was taking place through the patent ductus. Moderate cyanosis was present in this case and arterial oxygen saturation which was decreased to 82% rose to 100% after

murmurs whatever were present. Case 3 of the series reported by Keys and Shapiro⁹ was of this type. This 46 year old woman died of congestive heart failure. The blood pressure had been 142/40. The heart weighed 700 gm., and showed marked right ventricular and some left ventricular hypertrophy. A patent ductus 2 cm. long and 1.5 cm. wide was present without other congenital abnormalities. There was marked sclerosis of the ductus and pulmonary artery. The latter and its branches were also considerably enlarged. A plausible explanation of the absence of murmurs was that the pressure in the pulmonary artery was as great as in the aorta and therefore there was no flow

through the duct. There are also rare instances in which the characteristic murmur was noted to disappear in the last weeks of life.⁴ Here also a change in the dynamics of the circulation with severe heart failure may possibly account for the lack of flow through the duct.

Apical systolic murmurs were also invariably present in these cases of patent ductus arteriosus. Occasionally a short faint mid-diastolic murmur was present at the apex suggestive of mitral stenosis. These murmurs either disappeared entirely after successful operation on the ductus or there remained a slight pulmonary systolic murmur. The latter might persist for days or weeks and probably is due to the continued dilatation of the pulmonary artery or to the same indefinite mechanism involved in many inconsequential pulmonary systolic murmurs heard in healthy young individuals. When a basal diastolic murmur persisted after operation it was found to be due to recanalization of the ductus (in a few of the early cases in which the duct was ligated and not divided) or to bacterial endocarditis which had also involved the aortic valve.

Electrocardiograms proved very helpful in diagnosis. Despite the fact that right axis deviation is very common in various forms of congenital heart disease, there was only 1 instance in which definite right axis deviation was present (Fig. 6). In this case it was thought at first that another congenital abnormality was present in addition to the patent ductus. The fact that all murmurs disappeared after operation and no other evidence was elicited of further cardiac disease, the right axis deviation was thought to be due to concomitant pulmonary arterial disease and pulmonary hypertension. It is apparent, however, that the finding of right axis deviation should make one strongly suspect that the diagnosis of patent ductus is incorrect or that the patient has an additional lesion, such as pulmonary stenosis.

The diagnostic problem in exceptional cases may be very difficult. One instance, not included in this study, illustrates some points of interest. This young boy of 11 years had the classical machinery murmur at the base of the heart. The unusual feature was that it was much louder at the aortic than the pulmonary area. It was quickly surmised that he might have a persistent right aortic arch. The electrocardiogram, however, showed well-marked right axis deviation. At this point the diagnostic problem became too involved and it seemed advisable to study the problem by catheterizing the heart. This was done by Dr. Lewis Dexter³ and he was able to make a definite diagnosis of pulmonary stenosis, patent ductus arteriosus and right aortic arch. This was a very vital examination as it indicated not only that the ductus should not be sectioned, but that the congenital abnormality required that short circuit. The new operation devised by Blalock and Taussig had already been functioning in this case. If the ductus had been sectioned the boy could not have lived or at least the condition would have been made much worse.

Conclusion. A study was made of 37 verified cases of patent ductus arteriosus with special emphasis on the auscultatory findings before and after operation. The detection and proper interpretation of the murmurs are most important in diagnosis. Great variation in the intensity of the murmur was found and many failed to show the classical machinery character. In some the auscultatory findings were very inconspicuous.

Electrocardiography is indirectly helpful in diagnosis as only 1 case showed right axis deviation.

In doubtful or puzzling cases catheterization of the heart will be necessary to establish an accurate and definitive pre-operative diagnosis. Only in this way will some cases avoid harmful surgery.

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INFECTIOUS HEPATITIS: CLINICAL AND LABORATORY FEATURES
OF 295 CASES

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THERE have been excellent reviews of infectious hepatitis written by many prominent authorities. Although epidemics of the disease have been described for over a century, during the present war it has come into special prominence because of the high incidence among both civilian and military populations in all parts of the world. Infectious hepatitis is now thought to be caused by a virus. Present evidence suggests that transmission of the disease in epidemics may be by way of the gastrointestinal tract, although the respiratory tract as the important portal of invasion has been suggested. It is considered a systemic infection with the most prominent symptoms referable to the liver. While benign and rarely the cause of death, the disease can produce disablement for extended periods. This study is presented to illustrate the clinical features, laboratory data, treatment, and criteria for disposition of a group of cases of infectious hepatitis.

Procedure. This report is based on a study of 295 cases admitted to a general hospital in eastern France between February 15 and June 14, 1945. All patients were isolated. On the day after entry, the blood count, icterus index and urine examinations were performed. Blood icterus determinations and pigment studies of the urine were repeated at 3-day intervals throughout the hospital stay.

Other laboratory studies were performed as indicated. Patients were seen by the medical officer daily, and change in physical status and symptomatology noted at

frequent intervals. Length of hospitalization was determined by the clinical and laboratory features as well as by exercise tolerance as determined by a standardized reconditioning program. All patients were given a diet high in protein (2 grams per kilogram of body weight daily) and low in fat (less than 35 grams daily), the total calorie value being 2500 daily. The protein intake was supplemented by feedings between meals of skimmed milk enriched with egg albumin. Cooperation of the patients in partaking of this diet was excellent. Plasma was given liberally to patients who appeared severely ill or who were unable to eat. Patients were followed until discharge to duty. If after 60 days of hospitalization, recovery was incomplete, it became necessary to evacuate them from the theatre of operations.

Clinical Features. A number of different disease patterns were noted. The types and distribution are shown in Table 1.

Although the dominant form recognized was acute hepatitis with jaundice, which included all cases with icterus index above 12, a number of cases without jaundice were seen. Save for the milder course and the absence of jaundice in the latter, the two groups were identical. In patients with jaundice, the severity and duration of the illness was roughly proportional to the intensity of the icterus. A classification based on the intensity of jaundice is presented (Table 2).

Persistence of activity of the disease beyond 60 days was arbitrarily called subacute hepatitis, as this period was the

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maximum allowed for retention of patients in the theatre of operations. Although the tendency for this to occur varied with the peak icterus, even in the presence of hepatitis without jaundice it occurred in one-third of the patients.

The incidence of icterus of various intensity is shown in Fig. 1. The greatest number of patients fall in the range 40 to 49, with decreasing incidence at higher and lower levels. From this frequency distribution curve we are led to believe that the apparent incidence of hepatitis without jaundice is fairly represented at being in the neighborhood of 10%.

cases. Several other patients gave a history of isolated cases in their organizations antedating the general dissemination of the disease throughout the unit by 4 to 6 weeks.

ONSET. Although prominent in the onset of the disease was the well-known tetrad of anorexia, lassitude, epigastric distress, and dark urine, it was noted that the types of onset could be sharply categorized. While in two-thirds of the group the disease was ushered in with an array of symptoms suggesting influenza, in half of these patients the true diagnosis was suggested by the accompanying abdominal

TABLE 1.—CLASSIFICATION OF DISEASE PATTERNS

Disease Pattern Seen	Number of Cases
1. Hepatitis, acute infectious, with jaundice	260
A. With recovery within 60 days	142
B. With residual subacute hepatitis after 60 days	83
C. With relapse	35
1. With jaundice	14
2. Without jaundice	21
2. Hepatitis, acute, infectious, without jaundice	35
A. With recovery within 60 days	24
B. With residual subacute hepatitis after 60 days	4
C. With relapse	7
1. With jaundice	3
2. Without jaundice	4

TABLE 2.—CLASSIFICATION OF DEGREE OF SEVERITY BASED ON INTENSITY OF ICTERUS

Categories	Range of Icterus Index	Total Number of Cases	Number Requiring Over 60 Days	Per Cent
Very severe	Over 100	9	9	100
Severe	70-100	26	23	80.7
Moderate	40-70	111	50	45.0
Mild	10-40	114	36	31.6
Non-icteric	Below 10	35	11	31.3

INCUBATION PERIOD. Incubation period as estimated from this series falls into the accepted 3- to 6-week range. Two of the patients had been in this theatre of operations for only 5 weeks and with a unit in which an outbreak of hepatitis occurred, for only 25 days. Another group of patients were members of the organization which began drinking unchlorinated water directly after arrival at a new area; during the following few days many cases of diarrhea appeared, and 3 weeks later the first case of jaundice was noted, following shortly thereafter by a number of other

symptoms and dark urine. In the remainder of this group a few days elapsed before evidence of hepatic involvement was noted. In the patients showing an insidious onset, it was not uncommon for the first complaint to be dark urine, although the debilitating malaise and severe anorexia were usually more prominent. The small group complaining mainly of abdominal pain and anorexia were occasionally diagnostically troubling and at times simulated appendicitis or even renal colic.

SYMPTOMS. The frequency of various symptoms on entry are shown in Table 4.

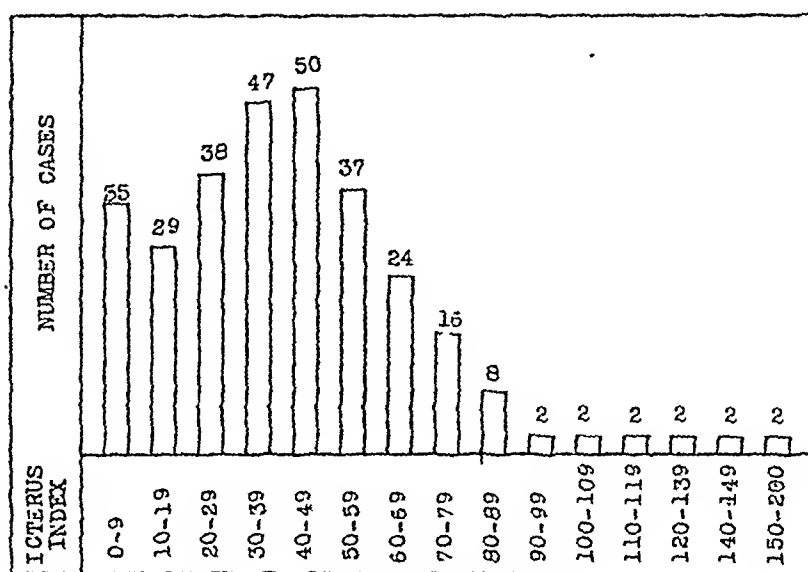


FIG. 1.—Distribution of peak icterus.

TABLE 3.—TYPES OF ONSET OF HEPATITIS IN 295 CASES

Types of Onset	Number of Cases	Per Cent
Influenzal (sudden onset, chills or chilly sensations, generalized aching, fever, headache, with or without respiratory symptoms).	95	32.2
Influenzal systemic symptoms with simultaneous signs and symptoms referable to the liver (fever, generalized aching, headache, anorexia, nausea, abdominal pain, dark urine).	99	33.6
Insidious (malaise, lassitude, anorexia, nausea, abdominal pain, dark urine).	86	29.2
Abdominal pain simulating the surgical abdomen.	15	5.1

TABLE 4.—SYMPTOMS AND SIGNS ON ENTRY IN 260 CASES OF HEPATITIS WITH JAUNDICE

Symptoms	Number of Cases	Per Cent	Signs	Number of Cases	Per Cent
Anorexia	250	96.2	Clinical jaundice	236	90.2
Dark urine	245	94.1	Skin and sclerae	210	80.0
Malaise	242	93.7	Sclerae only	26	10.2
Nausea	211	80.8	Tenderness in RUQ or epigastrium	223	85.7
Pain	178	68.4	Enlarged liver	180	69.1
Chilly sensations	159	60.9	Adenopathy	199	76.5
Headache	148	56.8	Generalized	101	38.9
Fever	138	52.2	Cervical only	98	37.6
Epigastric "lump"	125	48.0	Enlarged spleen	51	21.2
Vomiting	97	37.4	Bradycardia	105	40.2
Heartburn	71	27.4	Fever	188	72.0
Constipation	66	25.5	Rash	3	1.1
Itching	60	23.0	Herpes labialis	6	2.2
Alternating constipation and diarrhea	53	20.1			
Respiratory symptoms	53	20.1			
Chills	42	14.2			
Diarrhea	37	12.5			
Light stools	32	12.1			
Dysuria	30	11.9			

The same relative frequency was noted in patients without jaundice, save that in the latter dark urine was rarely described. In all, anorexia was almost invariable and usually severe. Abdominal pain was described by most patients as dull and leaden, by a few as sharp and colicky. Although usually noted as epigastric or right upper quadrant pain, it was frequently generalized. Many patients felt as though they had a "lump" in the epigastrium. A number complained of pain or a "tired" feeling in the back.

Dark urine was frequent, but only 1 patient in 8 reported light stools. Transient burning dysuria was occasionally noted. Six patients in 10 complained of disturbed bowel function, either diarrhea, constipation, or both. Headache, complained of on entry by 70% of the group was described by most as orbital or frontal; frequently the orbital pain was "burning", and patients noted aggravation of the pain on eye movement.

About half of the patients with an influenza type of onset had rhinorrhea, a few sore throat, and an occasional one complained of a cough. Most patients, however, suspected of having respiratory disease were under suspicion because of an undiagnosed febrile syndrome, rather than because of significant respiratory involvement. Five per cent of the group were admitted with a Roentgen-ray-verified diagnosis of primary atypical pneumonia.

Itching was noted on entry in 20% of the group. Transient urticaria was reported by 3 patients, labial herpes by 6 others.

SIGNS. The liver was palpably enlarged on entry in two-thirds of the group, averaging 2 cm. below the right costal margin; occasionally in extremely jaundiced patients it was at the level of the umbilicus. It was noted that often when the liver edge could not be felt in the right upper quadrant, careful palpation in the epigastrium demonstrated its enlargement.

Adenopathy, either generalized or cervical only was common. Barker¹ has placed some emphasis on the diagnostic helpful-

ness of a single enlarged node behind the right or left sternocleidomastoid muscle, but such limited adenopathy was found in only one patient. The nodes were usually small, averaging 1 cm., rarely twice this size, always soft and only slightly tender. The spleen, moderately enlarged in one-fourth of the group, was firm and non-tender.

Moderate bradycardia was noted in 40% of the group on entry, while fever, ranging from 99° F. to 101° F., was present in 70% of the patients. Occasionally it was higher, especially in the pre-icteric patient, rarely reaching 105° F. Clinical jaundice was noted on entry in 90% of the patients showing an elevated icterus index; of these one-ninth had scleral icterus only. Of the group not jaundiced on entry, a few had icterus indices between 10 and 13 at the peak; the remainder were pre-icteric on entry, developing their jaundice while in the hospital. These patients on entry were indistinguishable from the group classified as hepatitis without jaundice.

Skin lesions on admission were rare. Two patients showed a faint macular erythema of the face and chest and in 1 patient a papular eruption of the arms and trunk was noted.

COURSE AND DURATION. Symptoms observed during the hospital stay were essentially the same as those reported on entry. In general the abdominal pain, anorexia and headache complained of during the pre-icteric period decreased in intensity with the development of jaundice, but pain in the epigastrium, right upper quadrant, or small of the back persisted for 4 or 5 weeks in most patients. Pain and tenderness in one or both lower quadrants was noted in 10% of the group at some time during the hospital stay. Malaise and anorexia subsided gradually, the malaise often being the last symptoms to leave. Bloating was described by almost all patients during the 3rd, 4th and 5th weeks of hospitalization.

Itching, noted in only 20% of the group on entry; was complained of at some time during the course by 70% of the patients. Although mild and transient in most cases,

in a few patients it was severe and intractable for 3 or 4 days.

The liver usually remained palpable and tender as long as pain persisted. Jaundice receded at a rate paralleling the blood ieterus decrease.

Duration of signs and symptoms, although roughly proportionate to the intensity of the peak ieterus, showed a certain constancy. In 50% of the mild group there was disappearance of clinical and laboratory evidence of continued activity by the 5th week. Twenty per cent required 6 weeks for complete remission, while the remainder continued to present symptoms after 60 days of hospitalization. The shortest recovery period seen in patients with ieterus in the higher brackets was 6 weeks. The proportion of patients in each group not recovering within 60 days has already been shown (Table 2). Patients showing hepatitis without jaundice required approximately the same length of time for recovery and showed the same tendency to pass into the sub-acute stage as the group classified as mild.

Criteria used to determine recovery were modeled on those set forth by Barker¹. There included absence of pain or bloating, return of a feeling of well-being, absence of epigastric or right upper quadrant tenderness, subsidence of hepatomegaly (or if the liver remained enlarged, absence of tenderness) and presence of normal appetite. Laboratory evidences were a normal sedimentation rate, normal ieterus index for at least 2 weeks and urobilinogen in the first morning urine below the level of 2.0 mg. per 100 cc. With these criteria satisfied, the patients were subjected to an increasingly rigorous 10-day program of physical exercise. If all of the above features remained unchanged, the patient was ready for discharge to duty, without fear of relapse. Failure to adhere rigidly to all of these criteria early in the program necessitated re-admission of a number of patients who relapsed after being returned to duty. (See Case 123.)

RELAPSES. Most relapses were apparently due to excessive activity when the patient should have been at rest, too early

reconditioning, or intercurrent infections. There were, however, several cases which relapsed in the absence of any of these factors. In this group of 295 patients, relapses occurred in 43 cases, that is, 1 in every 7. There was no apparent correlation between the intensity of the original attack and the incidence of relapse, nor between the presence of intensity of jaundice in the original attack and the presence or height of ieterus in the relapse. One out of every 4 relapses was accompanied by jaundice. Three patients with typical bouts of acute hepatitis without jaundice, after 3 or 4 weeks of uneventful convalescence, relapsed and this time developed distinct ieterus.

In most cases the relapse was shown by return, after a symptom-free interval of a week or more, of pain, malaise and anorexia, and was verified by return of or increase in adenopathy and in size and tenderness of the liver. Laboratory correlation was found in return of, or increase in, urobilinogenuria, increase in serum globulin, and elevated sedimentation rate. When jaundice developed during a relapse, return of ieterus index to normal proceeded more slowly than in the initial attack.

Relapses were noted as early as 3 weeks and as late as 3 months after the initial attack. There were never more than 2 weeks of complete well-being between the end of the initial attack and the onset of the relapse.

COMPLICATIONS. No deaths were noted in this series. In 6 cases, however, the picture said ^{1,5} often to herald a fatal outcome was noted. This included sudden return of fever, extreme lethargy and drowsiness, severe nausea and vomiting. All 6 had been deeply icteric, but the time that this picture appeared varied from 1 to 4 weeks after the time of peak ieterus. To all such patients plasma and, at times, intravenous glucose were given liberally until definite improvement occurred. In addition to the above group, 21 patients showed transient behavior changes characterized by irritability, quernlousness, drowsiness, insomnia, and tremors. One patient developed an apparently typical

Guillian-Barre syndrome during the 4th week of the disease.¹⁶

It was noted that resistance to respiratory disease seemed slightly impaired in the patient convalescing from hepatitis. In 46 patients, about 15 % of the group, mild episodes of nasopharyngitis developed. Three other cases developed follicular tonsillitis.

Gingivitis was noted in 13 cases. Skin petechiae were observed in only 2 patients. Melena was noted in 3 cases and epistaxis in 2. Thirty-three patients developed

of symptoms. Rate of decrease of icterus was fairly constant and time required for return to normal is roughly dependent upon the peak achieved (Fig. 2). The longest period required for return to normal was 58 days, the peak icterus having been 180. There was no plateau, the peak was rapidly reached and recession of jaundice always started promptly.

HEMOGRAM. Study of the hemogram showed absence of anemia, normal total white blood count and a tendency toward reversal of the lymphocyte - neutrophil

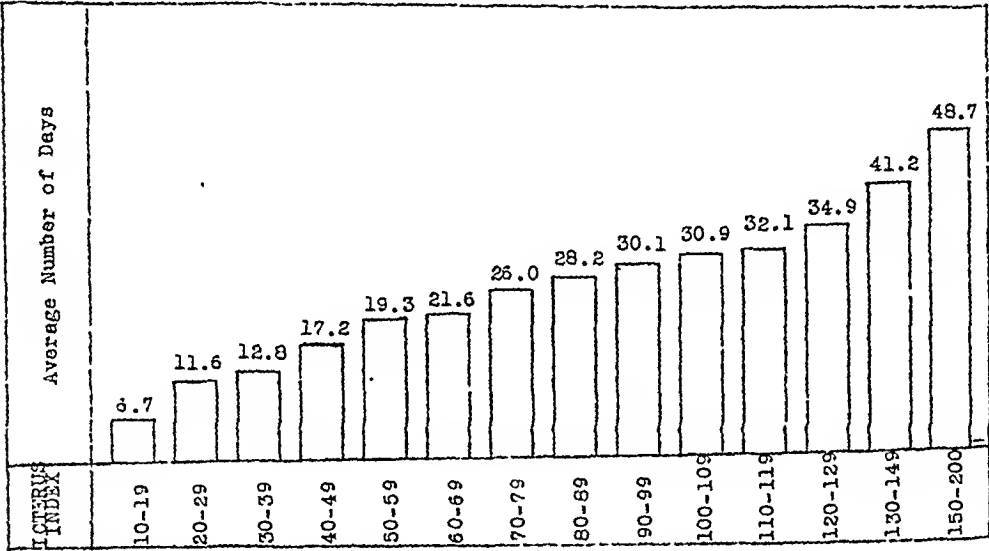


FIG. 2.—Relation between peak icterus and time required for icterus index to return to normal.

so-called "liver spots" during the 2nd and 3rd weeks of the disease. These were first seen as small (1 mm.) bright red areas on the arms, chest, and upper back which changed to brown in 24 to 48 hours. They became progressively darker during the following week, after which they remained relatively unchanged throughout hospitalization. No spider telangiectases were seen in the cases of acute hepatitis.

Laboratory Studies. ICTERUS INDEX. As indicated above, this test proved a rough measure of severity of the disease, and in general it was true that the longer the time required for return of icterus index to normal, the greater the duration

ratio (Table 5). A slight increase in eosinophils was noted in a considerable fraction of the group. This feature has not received emphasis previously. A check of patients with other diseases showed no abnormal concentration of eosinophils. Atypical lymphocytes which have been said to occur frequently in this disease were noted in 15 of 50 blood smears studied with this in mind.

SERUM PROTEINS. The level of serum proteins (copper sulphate method) and protein partition* was studied in 100 patients. It was found that 81 cases with clinical and other laboratory evidence of persistent disease activity showed a level

* Albumin was determined by precipitation with 22½% sodium sulphate followed by digestion and "Nesslerization," globulin by the difference between the total protein and albumin.

of serum proteins above 7 gm. per 100 cc. and serum globulin above 2.5 gm. Only 3 patients, apparently well by all other criteria, however, showed this abnormality.

SEDIMENTATION RATE. Sedimentation rate (Westergren) was normal during the early phase of the disease and if convalescence was complete, at the close of the period of hospitalization. On the other hand, during the 4th through the 8th week of the disease, if recovery was not complete, the sedimentation rate was moderately elevated (10 to 30 mm. per hour).

and for the pigmentary changes, the urine was normal. In an occasional deeply jaundiced patient, the picture of so-called "bile nephrosis" appeared transiently, with a low specific gravity, moderate albuminuria and bile-stained casts. Moderate glycosuria was noted on one or two occasions. Glucose tolerance studies of those patients failed to reveal any abnormality.

The significant urinary changes were those related to the pigment disturbance in this disease. The first voided morning specimen was found to be reliable for

TABLE 5.—HEMOGRAM IN INFECTIOUS HEPATITIS

	Hemogram 295 Cases	Number of Cases	Per Cent
White blood cell concentration	3-6000 per c. mm.	30	10.3
	6-8000 per c. mm.	118	40.0
	8-10,000 per c. mm.	132	44.6
	10-13,000 per c. mm.	15	5.1
Lymphocytes, number	50-60 per 100 WBC	84	28.5
	40-50 per 100 WBC	96	32.6
	30-40 per 100 WBC	81	27.5
	20-30 per 100 WBC	34	11.4
Neutrophils, number	70-80 per 100 WBC	10	3.4
	60-70 per 100 WBC	29	9.8
	50-60 per 100 WBC	78	26.4
	40-50 per 100 WBC	99	33.6
Monocytes, number	30-40 per 100 WBC	79	26.8
	0-5 per 100 WBC	55	19.7
	5-10 per 100 WBC	171	57.9
	10-15 per 100 WBC	69	23.4
Eosinophils	0-3 per 100 WBC	124	41.3
	3-5 per 100 WBC	97	32.9
	5-10 per 100 WBC	74	25.8

TABLE 6.—LEVEL OF SERUM GLOBULIN (100 CASES)

Status	Number of Patients	More than 2.5 Gm per 100 cc		Less than 2.5 Gm per 100 cc	
		Number	Per Cent	Number	Per Cent
With active disease	61	52	81.3	12	18.7
With apparent recovery	36	1	2.9	35	97.1

This proved a valuable criterion of fitness of a patient for reconditioning or discharge to duty, as well as often being the signal of a relapse.

KAHN. The Kahn examination was performed on the blood of 90 patients during the pre-icteric, early icteric and convalescent stages, as well as on the blood of patients in a relapse. In all cases the result was negative.

URINE. In the majority of patients, save for slight albuminuria during the pre-icteric and early icteric phase of the disease,

measuring bilirubinuria and urobilinogenuria⁵ and much less laborious than the 24-hour collection recommended by Watson.¹⁴ It has been shown that, using a modification of the Sparkman procedure for urobilinogen determination, the presence of more than 2.4 mg. per 100 cc. of morning urine is abnormal.⁸

The diphasic curve of urobilinogen excretion, described by others² in this disease, was noted in this study, with a pre-icteric rise in urobilinogen, and a drop as the icterus begins to recede. When jaundice

was extreme and biliruria massive, the urobilinogen at the time of peak icterus decreased to normal or subnormal levels, a situation simulating obstructive jaundice (Fig. 3). In the cases of hepatitis without jaundice, the diphasic curve is not seen, and unless a relapse occurs, there is a continuous decrease in urobilinogen level from time of entry into the hospital. Abnormal amounts of urobilinogen in the urine were not only often the first laboratory evidence of early hepatitis and incipient relapse in a convalescent, but also frequently served as an important laboratory aid confirming the diagnosis of hepatitis without jaundice.

The urine was examined for the presence of bile salts in 25 cases with deep jaundice, pruritus and bradycardia. In all but 2 cases the test was positive.

Although no attempt was made to assay the pigment content of the feces, it was noted that in 61 cases, or over 20% of the group, light stools were noted at the time of deepest icterus.

LIVER FUNCTION TESTS. The result of the *cephalin-cholesterol flocculation test* was studied in the first 75 cases, and although the test was positive in all cases, it was discarded as a means of following the patients when it was found that the blood of many apparently recovered cases, as well as of many apparently normal individuals, also gave positive readings. Whether this was due to lack of familiarity with the technique of the determination or to too highly sensitive a reagent cannot be stated.

Hippuric acid excretion after administration of oral sodium benzoate was tested in the same number of patients, but, like the cephalin flocculation test, proved of little value in this study. Many patients with obvious liver damage by other criteria showed normal hippuric acid excretion, while some who were apparently recovered continued to show apparent impaired ability to convert benzoic to hippuric acid.

Because of lack of materials and equipment, the dye excretion tests, serum phos-

phatase determination, cholesterol-cholesterol ester ratio and the prothrombin time determination were not attempted.

MISCELLANEOUS. To insure the fact that no cases of Weil's disease were being overlooked, 20 patients most closely simulating leptospirosis clinically were subjected to a study of the urine for the organisms and the serum for the specific agglutinins. The results were uniformly negative. Similarly, examination of the sera of 20 patients, whose blood showed a reversal of the neutrophil-lymphocyte ratio, failed to reveal the presence of the heterophil agglutinin seen in infectious mononucleosis.

Comment. The general clinical picture noted in this study is similar to that usually described. Ocular pain, however, was a more frequent component of the headache than was noted in Cameron's² series. Worthy of note in the present study were the distinct categories of onset, and the realization that influenza or respiratory disease may be simulated in the pre-icteric period. The relatively high incidence of itching and bradycardia in this series, while in contrast with the rarity of these symptoms in the group studied by Hayman and Reed,⁴ parallels the observations of Lucke⁶ and Cameron.² In conformity with this observation was the presence of bile salts in the urine of patients showing such symptoms.

Urobilinogenuria has been shown to be one of the most sensitive indices of liver function.^{10,11,14} A diphasic curve of urobilinogen excretion, with one rise in the pre-icteric period and another with decline of icterus has been reported by others² and noted in this series. Elevated urobilinogen levels in the urine serve as an extremely helpful clue for diagnosis before the appearance of icterus or in cases of hepatitis without jaundice. During the course of the disease, frequent determinations of the level help evaluate the progress of the patient, and when a rise in level occurs after previous return to normal, it serves to herald a relapse.

The observation^{1,15} that the sedimenta-

tion rate early in this disease is low or only slightly elevated, also noted in this series, is from the negative standpoint, a helpful diagnostic feature. In a patient with equivocal evidence of early hepatitis, the presence of a sedimentation rate above 15 mm. in 1 hour, renders the diagnosis unlikely or suggests the presence of some complicating disease. Paradoxically enough, during convalescence the sedimentation rate, when elevated, shows the presence of continued or renewed activity of the inflammatory process in the liver.

No "false-positive" serological tests for syphilis were noted. The Kahn test, performed at all stages of the disease, was uniformly negative.

The concept of hepatitis without jaundice has recently received emphasis.^{1,3,6,12,13} The proportion of cases of hepatitis which do not show jaundice reported by Barker¹ is far greater than that observed in the present study. Whether this apparent difference in incidence actually represents a difference between the two epidemics, or merely a difference in diagnostic criteria cannot be decided at this time. The diagnosis in this study was based on the occurrence of symptoms, physical findings and laboratory changes differing only in degree from those seen in cases of hepatitis with jaundice. Of significance was the occurrence of malaise, anorexia, epigastric fullness or distress, pain in the right upper quadrant or back, and tenderness in these areas with or without a palpably enlarged liver. The findings of increased urobilinogen levels in the urine and serum globulin in the blood confirmed the diagnosis.

Pre-icteric hepatitis and hepatitis without jaundice may present an identical picture and it is often impossible to predict whether jaundice will occur. The importance of the recognition of hepatitis without jaundice, when it occurs, lies in its potentiality of relapse and chronicity analogous to that of the cases of jaundice.

The criteria of recovery, as outlined by Barker¹ and applied in this study, are worthy of emphasis. Until the icterus index has returned to normal, disease is

still present. Attempts to start patients on physical activity before the icterus had been normal for at least 2 weeks almost invariably lead to relapse. Similarly, instituting physical exercise in a patient whose urobilinogen level is still above 2.0 mg. per 100 cc. of morning urine or whose sedimentation rate is above 10 mm. in 1 hour will usually lead to relapse. Of equal importance, although usually parallel with these laboratory features, are the clinical evidences of disease activity as outlined in the body of this paper. Finally, the acid test of the fitness of a patient for discharge from the hospital is his ability to tolerate physical exertion without the occurrence of symptoms, signs or laboratory evidence of a relapse.

It has been recommended that the treatment accorded hepatitis be a regimen of rest and rigid diet.¹ Bed rest during the acute phase of the disease and during early convalescence is of paramount importance; for inadequate bed rest and too early return to activity lead to relapses and to chronic hepatitis.

Recent studies⁹ have shown the importance to the liver of adequate protein intake. Since there was no control group, with respect to diet, used in the present study, evaluation of the efficacy of the high-protein, low-fat regimen is difficult. It was, however, noted that patients transferred from other wards, where they had been receiving a "regular diet", to the hepatitis section, experienced an increase in appetite and an amelioration of symptoms after several days of the "special" diet. Furthermore, the absence of deaths in this series may be significant. Since the mortality rate in this disease varies from 0.2% to 0.4%,⁵ it is difficult to predict whether in a series of the size studied here any deaths could have been expected. Nevertheless, several patients presented clinical and laboratory features similar to those considered prognostic of a fatal termination. Whether the survival of these patients was due to the high dietary protein regimen liberally supplemented by plasma cannot be determined.

The following case exemplified the insidious type of onset, the severity which this disease occasionally manifests, indications for the use of plasma, and the occasional simulation, from a laboratory standpoint, of "obstructive jaundice" (Fig. 3). The diphasic curve of urobilinogen excretion is also illustrated.

100 cc. The icterus index on entry was 48, the blood Kahn test negative and the sedimentation rate 6 mm. in 1 hour. Examination of the urine showed a specific gravity of 1.011, a "two plus" albuminuria, no sugar, and frequent bile-stained hyaline and granular casts. Bile was present and there were 15 mg. of urobilinogen per 100 cc. of urine. Bile salts were present in the urine.

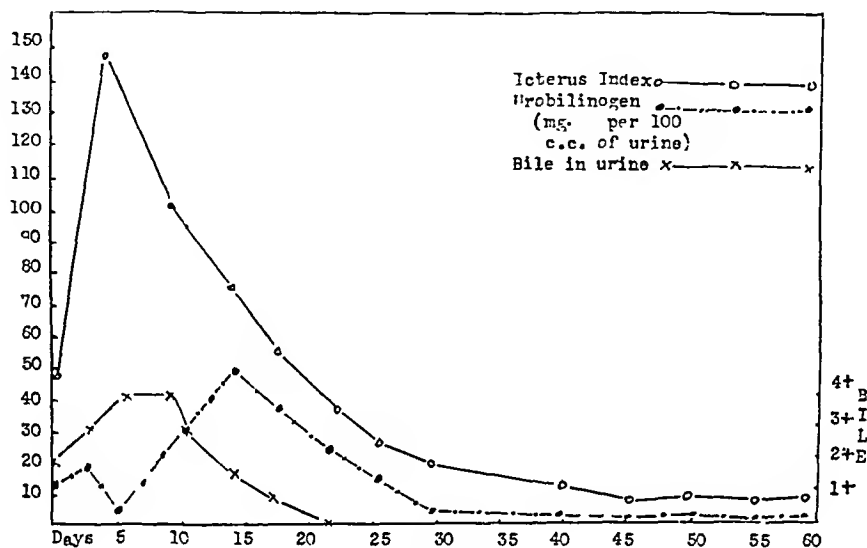


FIG. 3.—Case 105. A. L.

Case Reports. CASE 105. A. L., aged 24, was admitted to the hospital on March 21, 1945, with a history of gradual onset, during the preceding 12 days, of malaise, anorexia, and heavy, leaden pain in the epigastrium. Eight days before entry he noted dark urine, and, on the following day, he became constipated. On March 19th, he noted light stools, his skin began to itch and friends noted that he was turning yellow. Six weeks prior to entry he had had severe diarrhea for 1 week.

On entry he was moderately jaundiced, had enlargement of cervical lymph glands, and the liver edge, which was moderately tender, was 4 cm. below the right costal margin. Temperature was 98.2° F., pulse 52, and respirations 16.

The hemoglobin value and red blood cell count were normal (14.0 gm. and 4,800,000). There were 7,200 white blood cells per c.mm., of which 38% were neutrophils, 52% lymphocytes, 6% monocytes and 4% eosinophils. The serum globulin level was 3.1 gm. per

Course. The jaundice deepened rapidly, the liver descended to the umbilicus and anorexia remained moderate. On the 9th hospital day, anorexia became absolute and the patient became drowsy, irritable and developed nausea and vomiting. From the 9th through the 14th day, he was given infusions of 500 cc. of plasma daily. By the 14th day he was eating well and icterus was slowly receding. Improvement thereafter was slow but continuous. At the end of 60 days, because the liver was still enlarged and tender, and bloating, malaise and listlessness still present, he was evacuated to the Zone of the Interior.

The next case demonstrates the course of a mild hepatitis with jaundice. He was admitted to the hospital when jaundice was already receding, the first peak of urobilinogen was missed and the diphasic curve is not apparent (Fig. 4).

CASE 56. R. S., aged 26, entered the hospital on March 13, 1945, complaining of malaise and anorexia for 8 days. Before he lost his appetite, however, he had felt chilly and feverish for 1 day. Five days prior to entry he developed a dull aching in the epigastrium and a "tired" feeling in the back. Two days before admission the urine became dark. Early in February he had suffered a mild bout of diarrhea.

On admission he was moderately icteric. There was generalized enlargement of the lymph glands and a liver edge was felt just below the rib margin. Temperature was 98.8° F., pulse 58 and respirations 14.

tion rate were normal and liver edge was no longer palpable. After 10 days of reconditioning, when again sedimentation and urine were normal he was discharged to full duty.

The following case shows the course of laboratory findings in a patient who developed relapse with jaundice. Although most relapses seemed the result of excess or premature physical activity or intercurrent infection, this case relapsed in spite of absence of these factors (Fig. 5).

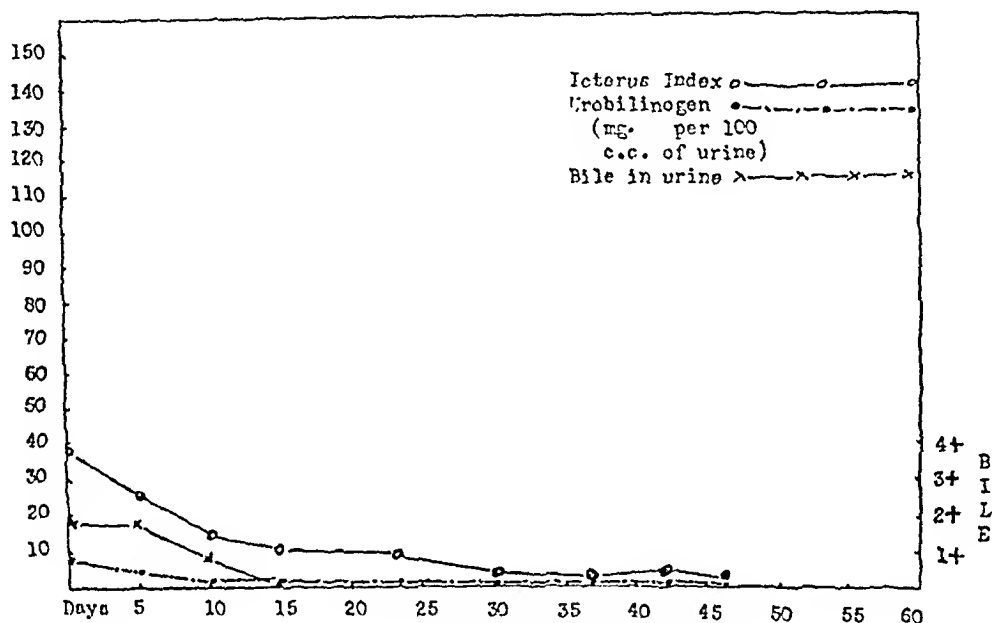


FIG. 4.—Case 56. R. S.

In the urine there was bile and 12.0 mg. of urobilinogen per 100 cc. Sedimentation rate was 11 mm. in 1 hour, and the Kahn test negative. There were 14.8 gm. of hemoglobin per 100 cc., 4,900,000 red cells and 6,400 white cells per c. mm. of blood.

Course. Jaundice gradually receded and by the end of the 3rd week had completely cleared. He began to eat well, on the 3rd hospital day his abdominal pain rapidly diminished and by the end of the 2nd week in the hospital had completely disappeared. Save for occasional bloating during the 3rd and 4th week, he had no further adverse symptoms. On the 36th hospital day, 2 weeks after return of his icterus index to normal, he was started on the reconditioning program. At this time urine and sedimenta-

CASE 114. J. J., 25 years old, was admitted to the hospital on March 18, 1945, with a history of malaise, anorexia, nausea, abdominal pain and dark urine for 10 days, and jaundice for 3 days. He had had a severe bout of diarrhea during the 3rd week in February. On admission he was moderately jaundiced, showed generalized lymph gland enlargement and a tender liver 3 cm. below the costal margin. Icterus index on entry was 56. There was marked bilirubinuria and urobilinogenuria.

Course. During the following 3 weeks jaundice, anorexia and abdominal pain receded gradually. On the 24th day of hospitalization, in spite of rigid adherence to the prescribed regimen of rest and diet, there was a return of epigastric distress and

loss of appetite. Urine showed increased urobilinogenuria, and icterus again began to deepen. Icterus index rose to a peak of 48 and then again began to recede. At the end of 60 days of hospitalization, because he was still complaining of epigastric fulness and bloating, and the liver was still tender and enlarged, he was evacuated to the United States.

recovered. The significance of even slightly abnormal urobilinogenuria as a criterion of incomplete recovery is well illustrated (Fig. 6).

CASE 123. R. A., aged 20, entered the hospital on March 16, 1945. Five days prior to entry he developed moderate fever, malaise, anorexia, nausea and dull leaden

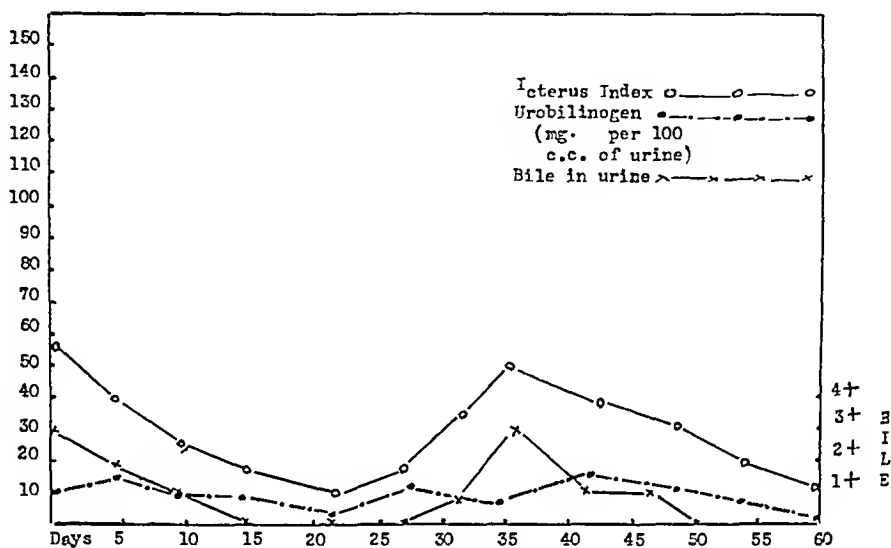


FIG. 5.—Case 114. J. J.

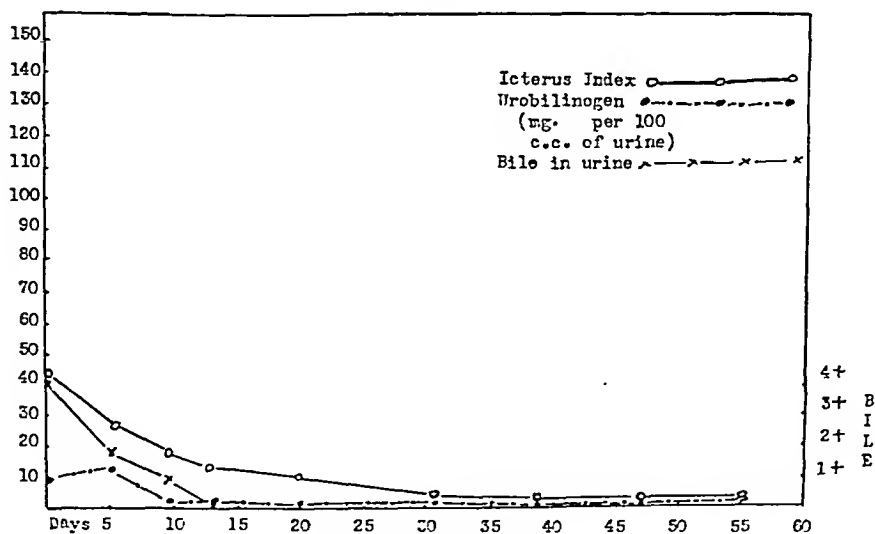


FIG. 6.—Case 123. R. A.

The next case demonstrates relapse without jaundice in a patient discharged from the hospital before he had completely

epigastric pain. On the following day he developed dark urine and on the day of admission skin jaundice was noted. On

admission he was moderately jaundiced. The liver was enlarged and tender. Icterus index was 44 on entry.

Icterus receded gradually and had disappeared by the 20th day. Urobilinogenuria dropped to normal levels by the end of the 4th week. He continued to have full epigastric distress and bloating and the tenderness persisted until the end of the 6th week in the hospital. At that time, with normal urine and sedimentation rate, he was subjected to a ten-day period of reconditioning. On the 56th hospital day, sedimentation was 9 mm. in 1 hour and the urine urobilinogen level was slightly above normal, and he was returned to duty. Ten days later he was readmitted to the hospital, having suffered a recurrence of right upper quadrant pain and anorexia 4 days previously which had grown progressively more severe. On entry he was listless, pallid (when discharged from the hospital, color had been good), the liver was again enlarged and tender. There were 6 mg. of urobilinogen per 100 cc., the sedimentation rate was 18 mm. in 1 hour, and there were 3.3 gm. of globulin per 100 cc. of serum. Although the urobilinogen level of the urine dropped to normal levels after 2 weeks of bed rest and "special diet" persistence of malaise, epigastric distress and tenderness as well as a continued high serum globulin necessitated evacuation to the United States.

The following case illustrates hepatitis without jaundice. Its clinical similarity to the forms with jaundice is evident.

CASE 125. R. S., aged 19, was a member of a unit with a high incidence of infectious hepatitis. On March 19, 1945, he was admitted to the hospital with a history of chills and fever for 2 days, pain in the right upper abdominal quadrant for 1 day. Five weeks previously he had had diarrhea for 6 days. On entry there was generalized enlargement of the lymph glands, tenderness in the epigastrium and the liver edge was felt 2 cm. below the costal margin. Temperature was 99.2° F., pulse 68, respiration 16. Hemoglobin and red blood cell values were normal. White blood cell count was 6,100, with 51% lymphocytes, 38% neutrophils, 9% monocytes and 2% eosinophils. Serum globulin level was 2.9 gm. per 100 cc., icterus index 9 units and sedimentation rate 12 mm. in

1 hour. In the urine there was a trace of albumin, 3.8 mg. of urobilinogen per 100 cc., but no bile nor other abnormalities.

Abdominal distress, moderate anorexia, size and tenderness of the liver and urobilinogenuria slowly receded. At the end of 2 weeks, urobilinogen levels were normal and at the end of 3 weeks all symptoms had disappeared. After 4 weeks in the hospital the liver was no longer palpably enlarged and there was no abdominal tenderness. He was given 10 days of physical exercise (reconditioning). At the end of this period with sedimentation rate and urobilinogen level normal, he was returned to duty.

The next case demonstrates the ability of a case of hepatitis without jaundice to develop icterus in a relapse. This potentiality again shows the identity of the non-jaundiced with those showing icterus (Fig. 7).

CASE 128. W. Y., aged 23, entered the hospital on March 28, 1945, with a history of fever and chills for 3 days, anorexia, nausea and abdominal pain for 2 days. On admission he was not jaundiced, had cervical lymphadenopathy, and a tender liver edge 3 cm. below the right costal margin. Temperature was 101° F., pulse 64, respirations 18. Hemoglobin and red blood cell count were normal. There were 5,400 white blood cells per c. mm. of blood, of which 46% were lymphocytes, 49% neutrophils, and 5% monocytes. Serum protein level was 7.3 gm. per 100 cc. of which globulin constituted 2.6 gm. The only urinary abnormality was the presence of 4.5 mg. of urobilinogen per 100 cc.

Symptoms and urobilinogen excretion gradually receded. At the end of 3 weeks he was feeling completely well and the urobilinogen level was normal. During the 4th week, although not authorized to do so, he began to indulge in physical activity. On the 26th hospital day he suffered a recurrence of anorexia and epigastric pain. On the following day increased amounts of urobilinogen were noted in the urine. Two days later clinical jaundice was noted. A peak icterus index of 48 units was achieved. Thereafter there was gradual recession of the icterus and symptoms. At the end of 60 days of hospitalization, anorexia and abdom-

inal pain persisted and he was evacuated to the United States.

Summary and Conclusion. The group was classified in terms of disease patterns seen depending on the presence or absence of jaundice, occurrence of relapses, and severity. The incubation period was estimated to fall within the accepted 3- to 6-week range. Onset was categorized on the basis of the insidiousness or rapidity

"liver spots" occurred. One patient developed a typical Guillain-Barre syndrome. A number of cases showed transient behavior changes.

The course of icterus and urobilinogenuria were described. The typical hemogram with absence of anemia, normal white blood count, but with a tendency to reversal of the lymphocyte-neutrophil ratio, and slight increase in eosinophils was de-

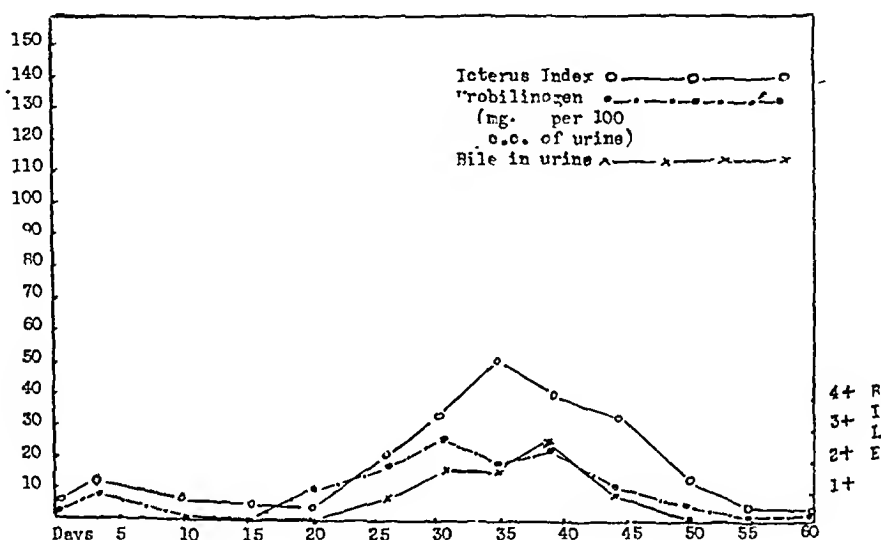


FIG. 7.—Case 128. W. Y.

of the symptom evolution, and presence or prominence of systemic and respiratory symptoms. Frequency of symptoms was shown with anorexia, dark urine, malaise, nausea, and abdominal pain most common. Jaundice, tender hepatomegaly, adenopathy and occasional splenomegaly were the significant signs.

Duration of signs and symptoms was rarely less than 5 weeks and many patients had residual disease after 8 weeks. Criteria for recovery have been outlined, and the necessity for rigid conformity to those criteria emphasized. The possibility and characteristics of relapses were discussed.

Although no deaths occurred, there were 6 cases which showed a clinical picture said to herald a fatal outcome. Most complications noted were mild. Gingivitis, skin petechiae, melena, epistaxis, and

scribed. The diagnostic and prognostic significance of an elevated serum globulin has been shown. The presence of bile salts in the urine of patients with deep jaundice, bradycardia, and itching was noted.

This report is another illustration of the prevalence of infectious hepatitis and its importance as a disabling disease of military personnel. The treatment followed has a firm theoretical basis and growing clinical supporting evidence. It is hoped that a realization of the need for adherence to this regimen and for careful use of the criteria of recovery will aid in preventing the sequelae and residua of hepatitis. Similarly the recognition and treatment of cases of hepatitis without jaundice are highly important in the prevention of chronic hepatitis.

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LIVER DYSFUNCTION IN RHEUMATIC HEART DISEASE

PRELIMINARY REPORT

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THERE has been considerable doubt as to just how much liver damage occurs as the result of heart disease, because passive congestion of the liver develops rather suddenly with the beginning of heart failure and frequently disappears just as quickly with the return of a normal circulation. The pathology of this condition was described by Fishberg³ as an engorgement of the central vein and adjacent capillaries, with the liver cells between the vessels soon becoming affected. These changes may advance to the degree that there is atrophy and replacement of the liver cells by fibrosis, which would make it reasonable to suspect that liver dysfunction occurs. This has been shown to be true not only in heart failure^{2,6} but Bingen and Stolte¹ found that a large percentage of a group of patients with acute and chronic rheumatic polyarthrititis exhibited deviations from the normal in various liver tests. In order to determine whether liver dysfunction occurs only at the time of heart failure or whether it is a gradually developing process, a series of 154 cases of rheumatic heart disease were studied, because in this type there exists a more easily measured period of time between the initial cardiac damage and heart failure. There was no special selection made in this entire group which was obtained by taking all cases as they presented themselves for examination. However, from this group 17 cases were eliminated because either by history or clinical evidence there was the slightest possibility of liver or gall bladder disease. All cases having any congenital cardiac lesion were

also eliminated. The remaining 137 cases were given the cephalin-cholesterol flocculation test as described by Hanger.^{4,5} We considered this test ideal because it has been shown that a cephalin-cholesterol emulsion was flocculated by serum from patients with active disturbances of the liver parenchyma and parallels the severity of the dysfunction. It may therefore be employed to estimate the degree or persistence of an active liver process. The test was always performed by the same technician and the results checked by one of us and plus-minus reactions were considered as negative.

Results. In the series of 137 cases of rheumatic heart disease there were 97 positive cephalin-cholesterol flocculation reactions (70%). The group was further subdivided into those cases that were or had been in heart failure at some time. There were 18 such cases with 15 positive reactions (84%). There were 17 cases of auricular fibrillation of which 14 showed positive reactions (82%) and in 5 cases of interventricular block all were positive (100%). Further inspection of this group revealed 4 cases of heart failure without any disturbance of rhythm or conduction of which 3 (75%) showed positive reactions. Of the cases of auricular fibrillation, all but 4 either were or had been in heart failure and of these 3 (75%) showed positive reactions. One of the cases of interventricular block also was in heart failure. The balance of the cases, 111 in number, were considered as of first and second degree cardiac function, and of these there were 75 showing a positive

reaction (67%). Grouped according to the vascular lesion present, they revealed positive cephalin-cholesterol flocculation reactions in 41 (77%) of 53 cases of mitral stenosis, 30 (64%) of 47 cases of mitral insufficiency, 24 (75%) of 32 cases of mitral stenosis and insufficiency, and 5 (55%) of 9 cases of aortic insufficiency. The remainder of the cases, few in number, had combined valvular lesions and therefore were not classified.

Table 2. It appears that after rheumatic heart disease has existed 1 year a positive cephalin-cholesterol flocculation reaction occurs and the number of years duration of the disease does not influence the percentage of positive reactions nor change the percentage from that of the entire group. The same close relationship of percentages were observed between the children and young adult cases under 20 years of age to the entire series when

TABLE 1.—AGE GROUPS AND CEPHALIN-CHOLESTROL FLOCCULATION TESTS OF 142 CASES OF RHEUMATIC HEART DISEASE

Years	Cephalin-Cholesterol Flocculation			Percentage Positives
	Positive	Negative	Plus-minus	
0-10	2	1	6	22
11-20	17	4	5	65
21-30	16	3	0	83
31-40	21	9	1	67
41-50	21	7	0	75
51-60	15	6	0	71
61-70	6	1	1	75

Plus-minus reactions were considered as negative.

TABLE 2.—APPROXIMATE DURATION OF RHEUMATIC HEART DISEASE AND CEPHALIN-CHOLESTROL FLOCCULATION TESTS IN 128 CASES

Years	Cephalin-Cholesterol Flocculation			Percentage Positives
	Positive	Negative	Plus-minus	
0-1	0	1	3	0
1-2	7	3	0	70
2-4	4	0	1	80
4-6	3	3	1	43
6-10	10	0	1	90
10-15	9	3	0	75
15-20	22	4	0	84
20-25	10	3	0	76
25-30	9	4	1	64
30-35	9	0	0	100
35-up	13	4	0	76

Duration estimated from etiological attack or when heart disease was first recognized.

Plus-minus reactions were considered as negative.

The age range in the entire series of cases of rheumatic heart disease was from 7 to 67 years. In order to determine whether or not aging had any relationship to this phenomenon the cases were subdivided into decades as shown in Table 1. This, however, does not give any information as to how long rheumatic heart disease must be present before positive cephalin-cholesterol flocculation reactions are obtained. There were 128 cases in which it could be ascertained with a relative degree of certainty the number of years this disease had been present and these were divided into time periods as shown in

they were subdivided according to the valvular lesion present. The positive reactions were 5 (45%) in 11 cases of mitral insufficiency, 6 (86%) of 7 cases of mitral stenosis and insufficiency, and 4 (80%) of 5 cases of mitral stenosis. None of these cases was in heart failure nor had auricular fibrillation; however, in 2 cases with auricular fibrillation there were positive reactions.

The group of 97 cases were investigated as to whether there was any correlation between the degree of cephalin-cholesterol-flocculation-positive reactions and the severity of the rheumatic heart disease.

The 22 positive reactors with auricular fibrillation, heart failure or interventricular block were divided as follows; 13 were plus 1 or 2, and 9 plus 3 or 4, and the 75 positives in cases of slightly to moderately advanced rheumatic heart disease were 39 plus 1 or 2, and 36 plus 3 or 4. There did not appear to be any relationship between the degree of positive reaction and the degree of heart disease.

Summary. 1. The cephalin-cholesterol flocculation reaction was found positive in 72% of 136 cases of rheumatic heart disease.

2. The cephalin-cholesterol flocculation reaction was positive in 89% of the cases with heart failure, 82% of the cases with

auricular fibrillation and 100% of those with interventricular block.

3. The cephalin-cholesterol flocculation reaction was positive in 69% of 110 cases of rheumatic heart disease considered as of first or second degree cardiac function.

4. Neither the valvular lesion, age of the patient nor the length of time rheumatic heart disease existed seemed to effect any variation from the percentage of positives of cephalin-cholesterol flocculation reactions in the entire group.

5. There was no correlation found between the degree of positive cephalin-cholesterol flocculation reaction and the degree of functional severity of rheumatic heart disease.

The authors wish to thank 1st Lt. H. V. Bieghler of Strouthers, Ohio, for his assistance in preparing this report.

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THE TREATMENT OF PNEUMOCOCCIC PNEUMONIA WITH ORAL AND INTRAMUSCULAR PENICILLIN

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THE value of penicillin in the treatment of pneumococcic pneumonia has been amply demonstrated. Numerous reports^{1,3,7,8,10,13} attest to its effectiveness when it is administered by the intramuscular route. The results in a relatively small number of patients with this disease who have been treated with this antibiotic by oral administration have been good.^{2,6,11} Since the oral route is more desirable for the patient and since it does not require hospitalization or special nursing care, it would be the method of choice in most instances if the physician could be certain that the results would be as good as when parenteral methods were used. In an effort to answer this latter question we have treated comparable groups of patients with penicillin by the intramuscular and oral routes.

METHOD. Blood for culture and sputum for pneumococcus typing were obtained from all patients admitted to the medical wards of the Gallinger Municipal Hospital who were diagnosed as having pneumonia. The patients were then given either 15,000 units of penicillin intramuscularly every 3 hours or 75,000 units by mouth at the same intervals. The two routes of administration were used without any selection of cases except that the oral preparation was employed when it was available and the intramuscular route at other times. One patient who was scheduled to receive penicillin orally was given the drug intra-

muscularly instead, because he was comatose on admission. His case has been placed in the oral group in our calculations.

The intramuscular preparations used were various lots of commercial penicillin G (in 73 patients), crystalline penicillin G* (in 34 patients), and penicillin X† (in 3 patients). The oral doses were usually given in the form of tablets containing 25,000 units of sodium penicillin buffered with calcium carbonate.† Penicillin treatment was continued until the temperature had fallen and remained at or below 100° F. for 2 to 4 days.

Results. Since no significant differences were observed in the results obtained with the use of commercial penicillin G, crystalline penicillin G, and penicillin X intramuscularly, the patients treated with these preparations have been placed in one group for the purposes of this paper. A comparison of the therapeutic effects of these preparations in various diseases including pneumococcic pneumonia is being published elsewhere.¹² It will be seen from Tables 1 and 2 that the groups of patients treated by the two routes were comparable with respect to the types of pneumococci causing the disease and were essentially similar in respect to age distribution. The incidence of bacteremia was somewhat higher in the group of patients who received penicillin intramuscularly and there was a slightly larger proportion of patients

* Supplied by Merck and Company, Rahway, N. J.

† Supplied by the Lederle Laboratories Incorporated, Pearl River, N. Y.

above the age of 50 years in the intramuscular-treatment group.

There were 59 patients in the oral-treatment group, of whom 3 (5.1%) died. Among the 190 patients in the intramuscular-treatment group, there were 9 deaths (8.3%). This difference is not considered significant, in view of the fact that there was a greater proportion of patients in the older age-groups in the intramuscular-treatment group. Furthermore, there were 6 patients with bacteremia treated with oral penicillin, 2 of whom died, and 18 bacteremic patients given intramuscular penicillin among whom only 3 died.

The first day is almost identical among the patients treated with oral and the patients treated with intramuscular penicillin (57% and 59% respectively). By the end of the 2nd day after treatment was started, the figures for the 2 groups were 86 and 85% for the oral-treatment and intramuscular-treatment groups, respectively. Thus it appears that there was very little difference in the rate at which the temperature fell, regardless of whether the penicillin was given by mouth or by intramuscular injection. This similarity is illustrated by Figures 1 and 2 which portray representative temperature charts from patients

TABLE 1.—RESULTS OF TREATMENT WITH PENICILLIN ORALLY AND INTRAMUSCULARLY, ARRANGED ACCORDING TO TYPE OF PNEUMOCOCCUS

Type of Pneumococcus	Oral Penicillin				Intramuscular Penicillin			
	All Cases Number	Died	Bacteremic Number	Cases Died	All Cases Number	Died	Bacteremic Number	Cases Died
1	7	1	2	1	12	1	6	1
2	8	0	1	0	12	0	1	0
3	9	0	0	0	13	3	3	2
4	3	0	1	0	6	0	2	0
5	2	0	1	0
6	5*	1*	0	0	4	0	0	0
7	9	0	1	0	18	0	3	0
8	8	1	0	0
Other types . . .	14	1	1	1	27	2	2	0
No type obtained .	4	0	0	0	6	1	0	0
Total	59	3	6	2	109	9	18	3
		(5.1%)		(33.3%)		(8.3%)		(16.7%)

* One patient received intramuscular penicillin because he was in coma.

TABLE 2.—RESULTS OF TREATMENT WITH PENICILLIN ORALLY AND INTRAMUSCULARLY, ARRANGED ACCORDING TO AGE OF PATIENTS

	Oral Penicillin		Intramuscular Penicillin	
	Number	Died	Number	Died
12-20	5	0	10	0
21-30	14	0	24	0
31-40	20	2	28	1
41-50	8	0	21	1
51-60	8	1	9	2
61-70	3	0	7	1
over 70	1	0	10	4
Total	59	3	109	9

One method which we^{4,5} have found useful in comparing the results obtained in patients with pneumococcal pneumonia treated by various drugs is to determine the rapidity with which the temperature falls and remains below 101° F. among the patients who have recovered. From Table 3 it will be seen that the percentage of patients who experienced a crisis within

receiving this antibiotic by the 2 methods of administration.

In addition to the case fatality rate and the rate of temperature fall, another important method of judging the value of a drug in pneumococcal pneumonia is its effectiveness in preventing complications. Six of the patients treated with penicillin orally, and 16 of those who received it

intramuscularly, developed complications. None of these complications were serious nor were they the cause of death in any instance. One patient was classified as having developed empyema because 30 cc. of cloudy fluid were removed from his pleural cavity on the 4th day of treatment. Although the fluid was purulent, direct

signs or roentgenologic evidences of pleural fluid appeared, additional thoracenteses were not performed. Subsequent recovery was without incident.

Discussion. When similar doses of penicillin are administered orally and intramuscularly the blood concentrations obtained with the former method are not as

TABLE 3.—RAPIDITY OF CRISIS IN RECOVERED PATIENTS

	Number of Patients	Oral Penicillin Per cent of Recovered Patients	Intramuscular Penicillin Number of Patients	Per cent of Recovered Patients
Temperature 101° F. or below, within:				
0 to 23 hours	30	57	59	59
24 to 47 hours	16	29	26	26
48 hours and over	8	14	15	15
All Recovered Patients	56	100	100	100

TABLE 4.—COMPLICATIONS OF PNEUMONIA

Complication	Patients Receiving Oral Penicillin	Patients Receiving Intramuscular Penicillin
Pleural Effusion	1	2
Empyema	1	0
Delayed Resolution	2	9
Spread into Another Lobe	0	2
Relapse	1	2
Otitis Media	1	1

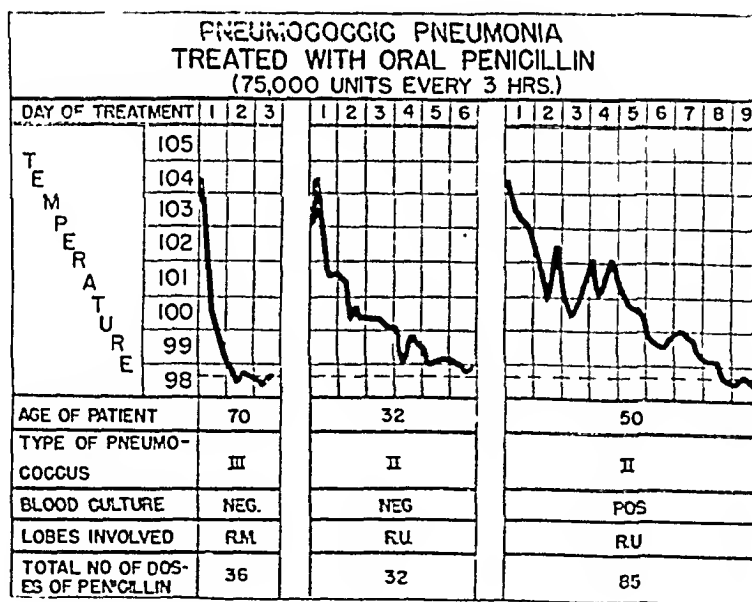


FIG. 1.

smear and culture revealed no organisms. At the time of the thoracentesis, an attempt was made to inject 50,000 units of penicillin into the pleural space but this could not be done, since the cavity was filled by the quantity of solution which contained 5,000 units. Since no further

high as those obtained following intramuscular injections. McDermott and his co-workers⁹ have shown that the chief reason for this fact is that only a small portion of the penicillin is absorbed from the gastrointestinal tract.

It has been recommended that oral

penicillin should be given in doses 3 to 5 times as great as those employed by the intramuscular route because of this irregular absorption. Bunn and his associates² treated 45 patients with pneumococcic pneumonia by the oral administration of 200,000 units initially followed by 50,000 units at 2-hour intervals. One patient in this group died and 1 developed empyema. Finland and his co-workers² gave 150,000 to 300,000 units initially and 90,000 or 100,000 units every 2 hours to 7 patients, all of whom recovered. Ross and his associates² observed recovery in the case of 2 children whom they treated with 100,000 units at 3-hour intervals.

Oral therapy is preferable when it is not feasible to give multiple injections (as in the treatment of patients at home) or when the patients object to the frequent injections. Administration of penicillin by injections in beeswax and oil may be said to occupy a middle ground between the other 2 methods. This preparation need not be given as often (every 12 or 24 hours) but is more expensive than the products given by multiple injections, as expensive, in fact, as giving larger doses orally.

The results obtained in pneumococcic pneumonia with the use of penicillin by either method were excellent. The total

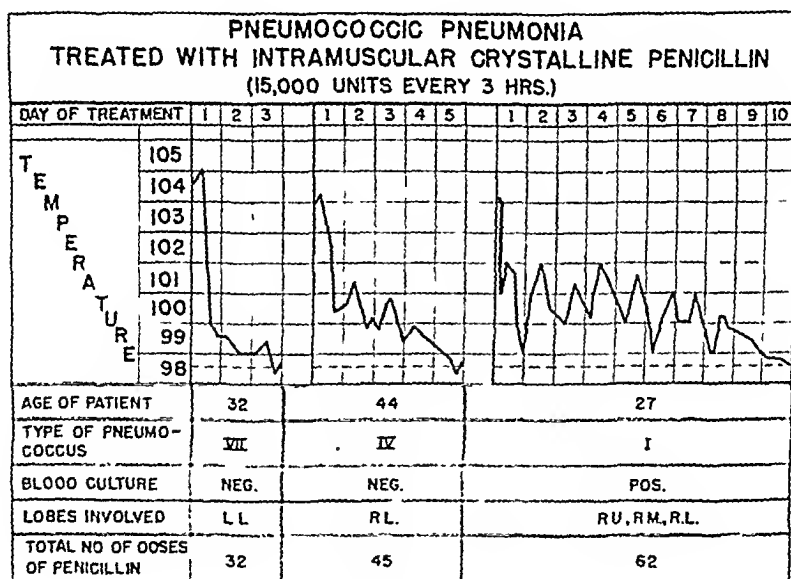


FIG. 2.

We decided to administer to our patients either 15,000 units intramuscularly or a dose 5 times as great, 75,000 units, orally. The results, as judged by the case-fatality rate, rapidity of temperature-fall and incidence of complications, were similar in the 2 groups. As a result of these observations, the indications as to the route of administration of penicillin in patients with pneumococcic pneumonia may be stated as follows: intramuscular therapy is preferable when cost is a major factor or when the patient is comatose or uncooper-

number of patients treated with penicillin was 168 and the total number of deaths 12, giving a case fatality rate of 7.1 %.

We would like to stress 2 additional facts about the oral administration of penicillin: First, it seems best in view of the evidence available at present, that the oral route should not be used for the treatment of the more severe infections, such as bacterial endocarditis, staphylococcic bacteremia and pneumococcic meningitis. Second, when penicillin is administered orally it should always be given in large

doses, preferably 5 times as large as those which would be given intramuscularly in the treatment of the same infections.

Summary and Conclusions. 1. Among 168 patients given penicillin for pneumococcal pneumonia 12 (7.1%) died. Fifty-nine of these were selected (upon the basis of the availability of the oral preparation) to receive penicillin by mouth in doses of 75,000 units every 3 hours, and of these 3 (5.1%) died. Another group of 109 patients were given penicillin by intramuscular injections of 15,000 units every 3

hours. Among these 8 (7.4%) died. The rapidity of crisis and the incidence of complications were approximately the same among the patients in the oral-treatment and intramuscular-treatment groups.

2. It is concluded that patients with pneumococcal pneumonia may be treated with penicillin administered orally if large enough doses are given. Doses of 75,000 units given every 3 hours until the temperature has fallen and has remained below 100° F. for 48 to 96 hours are satisfactory for routine treatment.

We wish to thank Dr. George C. Ruhland, Dr. James G. Cumming, and Dr. John E. Noble for their cooperation, and Dr. J. B. Holland, Miss C. Barbara O'Neil and Miss Helen Wright for technical assistance.

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SOME PHARMACOLOGICAL AND CLINICAL EXPERIENCES WITH
DIMETHYLAMINOETHYL BENZHYDRYL ETHER
HYDROCHLORIDE (BENADRYL)*

BY THOMAS H. MCGAVACK

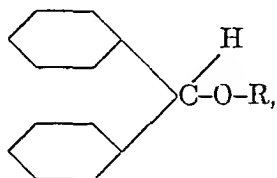
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FOLLOWING the demonstration that a series of benzydryl ethers of the general formula



could prevent fatal anaphylactic shock from histamine inhalation in guinea pigs,^{31,32} further studies^{33,34,35,36,52} have shown its antihistamine action to be more than 600 times that of papaverine. In addition some atropine-like and anticholinergic effects have been observed.^{6,9,35,52,53} The clinical implications of these facts have been quickly recognized, particularly in relation to the control of allergic manifestations in the skin.^{7,8} The occurrence of unpleasant symptoms in these and other⁵² early clinical experiences with the drug has raised the important question of toxicity as applied to human beings. Therefore, carefully controlled observations of normal individuals receiving the drug in several times the originally recommended doses have been made. In each subject the various systems of the body have been closely watched and their functions thoroughly appraised. In a previous communication,⁴¹ the scope of the above mentioned survey together with early clinical experiences have been detailed. The purpose of the present report is threefold: (1) to emphasize the positive pharmacological data as gained from the admin-

istration of the drug to normal healthy human beings and to patients; (2) to evaluate, at least in part, the therapeutic range of activity of "Benadryl," and (3) to record the unpleasant symptoms or side-effects of "Benadryl" with an analysis of their nature and frequency.

Methods and Materials. More than 60 normal persons and 242 patients have been the subjects of these observations. Of the normal subjects, 21 have been subjected to a complete cycle of examinations pertaining to the major systems and functions of the body. The remainder have been used for the elucidation of one or more of the special pharmacological problems, such as the effects of the drug on the eye or on glucose tolerance. In all normal subjects the standardization of living routine was as previously described.⁴¹ Intravenous glucose tolerance curves were performed according to the method of Thorn⁵⁵ slightly adapted to our own needs.⁴⁷ Values for "Benadryl" in the blood and spinal fluid were determined by the method originally described by Brodie⁴ with some modification.¹⁸ Methods for all other laboratory procedures have been given in detail elsewhere.⁴¹ The majority of all observations were made following the oral administration of the drug. In addition, glucose tolerance curves and blood pressure readings were obtained following a single intravenous dose of 20 to 30 mg., and the effects upon the eye were recorded pursuant to its topical application.

Results. I. PHARMACOLOGICAL DATA.

1. *The Antihistamine Effects.* Repeatedly,

* Read in part before the Research Session of the New York Academy of Medicine, May, 1940.

the unpleasant reaction which sometimes attends the administration of histamine in the course of gastric analysis was relieved by the intravenous administration of 20 mg. of "Benadryl." Thus we confirmed in human beings the observations made on small laboratory animals by Kaiser, Lowe and their co-workers.^{31,36}

from 150 to 400 mg. daily over periods ranging from 1 to 18 weeks. The results are summarized in Table 1. The variability of this response is illustrated in Fig. 1, and shows the necessity for individualization of dose in each patient. Apparently the severity of this reaction bore no relationship to the patient's clinical con-

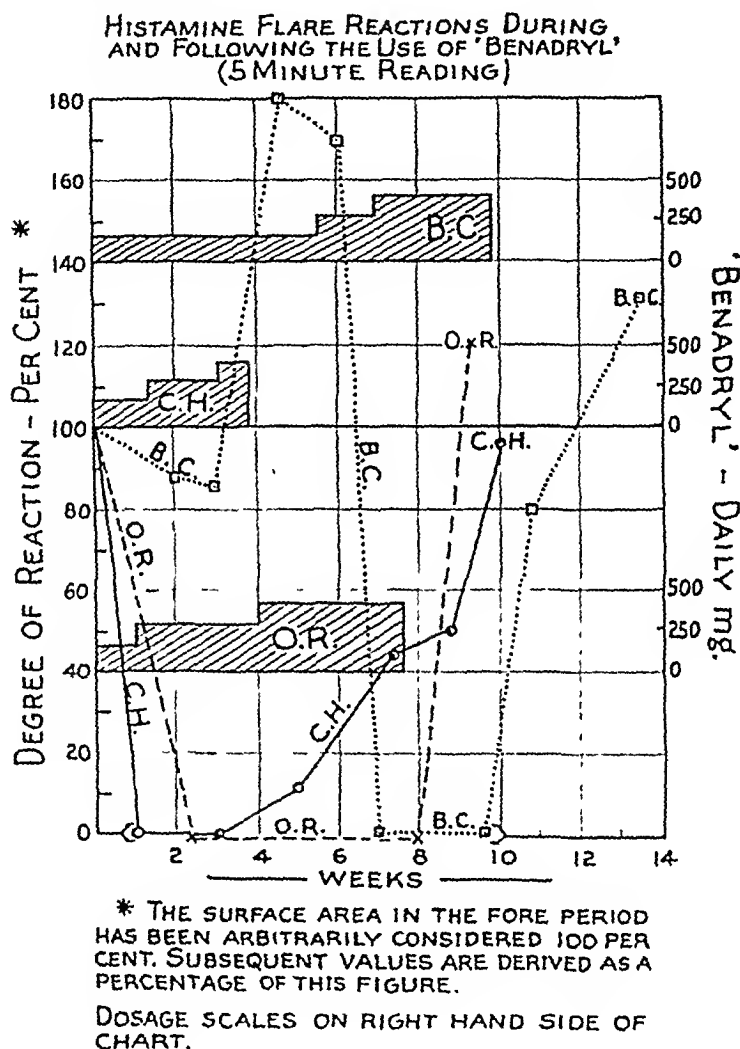


Fig. 1.

More specifically, this antihistamine effect was demonstrated in relation to the oral administration of "Benadryl" at various dosage levels in the following ways:

(n) Suppression of the dermal response to histamine. The wheal and flare responses of 20 normal subjects and 7 patients were recorded following the oral administration of "Benadryl" in doses of

dition, nor to the presence or absence of some allergic disease. For instance, O. R. (Fig. 1) was an asthmatic of long standing, while B. C. (Fig. 1) and C. H. (Fig. 1) were normal individuals. Despite these wide variations in response from individual to individual it was possible to suppress completely the reaction in any given subject by some dosage well within the therapeutic range. Indeed, the uniform-

ity with which this response could be elicited strongly emphasizes the antihistamine character of "Benadryl" activity and the satisfactory results which have been obtained in a wide variety of skin conditions.^{2,7,8,14,15,30,33,39,44,50,51,56,57,61,62}

(b) The depression of gastric acidity. Almost as impressive as the influence of "Benadryl" upon the dermal response to histamine was its ability to suppress the secretion of acid by the stomach. As was the case with the "flare and wheal reaction," the daily dose and period of administration necessary to bring about this effect varied widely from subject to subject, but was produced with a single exception in each of 21 subjects upon whom tried. This particular patient responded with a decided increase in

or pretreatment gastric analysis have been accepted as 100 per cent in each instance, and subsequent values reckoned as a percentage thereof. The composite curve shown is the averaged value of these percentages.

When "Benadryl" is stopped, from 1 to several weeks are required for the secretion of gastric acid to return to normal. In some instances, the anacidity or hypoacidity gives way to hyperacidity in this release phase.

Inasmuch as histamine has now been accorded an important place in the secretion of gastric acid under physiological conditions,^{1,16,46} the suppression of acidity following the administration of "Benadryl" is rather convincing evidence of its antihistamine activity.

TABLE 1.—ERYTHEMA AND WHEEL REACTIONS TO INTRACUTANEOUSLY ADMINISTERED HISTAMINE DURING AND FOLLOWING "BENADRYL" THERAPY

No. Subjects	27	11	18	5	9	4	3
Dosage (mg. Daily)	0	150	300	400	0	0	0
Duration Treatment (weeks)	2.3	3.5	4.0	1.0	2	5
Degree of Reaction:							
Erythema:							
5 min..	100	25	0	0	6	73	138
10 min..	100	11	0	0	15	92	138
Wheal:							
5 min..	100	18	0	0	2	80	120
10 min..	100	14	0	0	17	88	132

gastric acidity, most marked when 400 mg. of drug were given daily; gastric acidity returned to normal within two weeks after the drug was discontinued.

As a rule the change in gastric secretion could be observed within one week after administration of the drug was begun in a daily dose of 150 mg., but in some subjects as much as 400 mg. daily for 2 weeks was necessary to elicit it. It was usually possible to suppress completely the formation of acid by the stomach, in from 1 to 4 weeks when 400 mg. were given daily. For the majority of these subjects the data are fully analyzed elsewhere.^{40,41} The averaged results in 5 normal subjects who received 400 mg. of "Benadryl" daily for 3 to 5 weeks are illustrative (Fig. 2). In making these curves, data from the initial

(c) The decrease in capillary permeability. As determined by fluorescein,²⁸ the permeability of the capillaries of the lower extremities was decreased by large doses (300 to 400 mg. daily) of "Benadryl" (Fig. 3). Moreover, in a negative way it has been shown that meningeal capillaries, normally more or less resistant to the passage of fluorescein, are not appreciably influenced in this respect by "Benadryl",⁴¹ despite the fact that this drug readily diffuses into the spinal canal to establish levels comparable to those in the blood.¹⁸

That histamine has a normal role to play in the permeability of tissue capillaries was suggested many years ago. Moon⁴² has more recently summarized some of the evidence confirming such an activity. It, therefore, seems logical to

conclude that "Benadryl" probably "tightens" the capillaries through a neutralizing action upon the histamine of the tissue.

2. *The Atropine-like Activity.* The anti-histamine activity of "Benadryl" has been fully confirmed by a number of observers.^{6,9,10,11,12,13,15,31,32,33,34,35,40,41,45,49,52,58,69,60}

This is, indeed, the only action of the drug which can be distinguished with certainty.

solution of 0.5% or more. No changes were apparent when the drug was given orally up to 400 mg. daily for several weeks, except for a slight blurring of vision in 10 of 242 patients. In 60 subjects the eyes responded to the topical application of a 0.5% aqueous solution of "Benadryl" by an increase in the size of the pupil in 49, a decrease in visual acuity in

INFLUENCE OF BENADRYL ON GASTRIC ACIDITY 400 MG. DAILY FOR 3.5 WEEKS

DATA EXPRESSED IN PERCENTAGE OF
"FORE ANALYSIS"

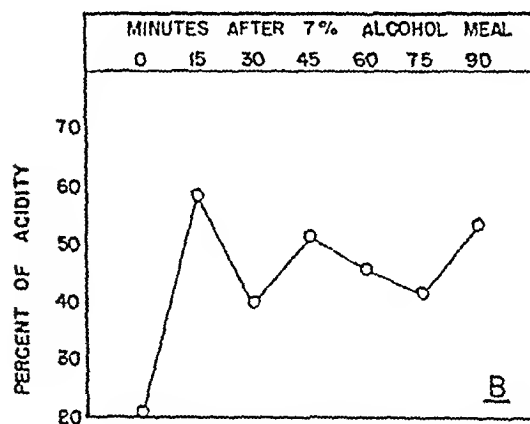
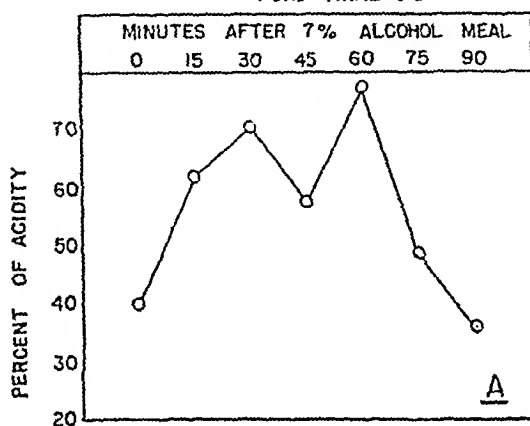


FIG. 2.—A, total acid; B, free acid.

However, attention has been directed also to both an atropine-like effect^{6,21,25} and to an anti-acetylcholine influence.^{9,52-53} Nevertheless, one must tread cautiously in allocating any particular observation to either one or both of these categories. In the data here presented, a clearcut atropine-like influence seems to have been exerted upon the human eye by the local application of "Benadryl" in an aqueous

12, and a decrease in ability to accommodate in 43.

In 25 subjects, the effects upon pupillary diameter of "Benadryl" alone and of "Benadryl" in combination with epinephrine, homatropine and eserine, respectively, were compared (Fig. 4). The readings on which this chart (Fig. 4) is based were made at the end of 1 hour; the full technic of the tests has been

described in detail elsewhere.²¹ Within the limits of experimental error the dilating action of "Benadryl" was not increased by epinephrine, but the speed with which it occurred was hastened so that the response became maximal within 15 minutes instead of 1 hour. "Benadryl" appreciably furthered the mydriatic action of homatropine (from 150 %–169 %) and antagonized the miotic influence of eserine by increasing the pupillary aperture from 38 % of its pretreatment size to 50 % of that value.

here to emphasize the point that, unlike sympathomimetic drugs, it may produce a quieting rather than an erethistic effect. Moreover, when large doses of the drug are used (200 or more mg. at a single dose or 600 or more mg. daily), some of the effects upon the sensorium closely resemble those of the belladonna alkaloids.

(a) Action on the cardio-vascular system. No disturbances in pulse rate or size of the capillaries was observed in subjects receiving from 150 to 600 mg. daily. As previously mentioned, capillary perme-

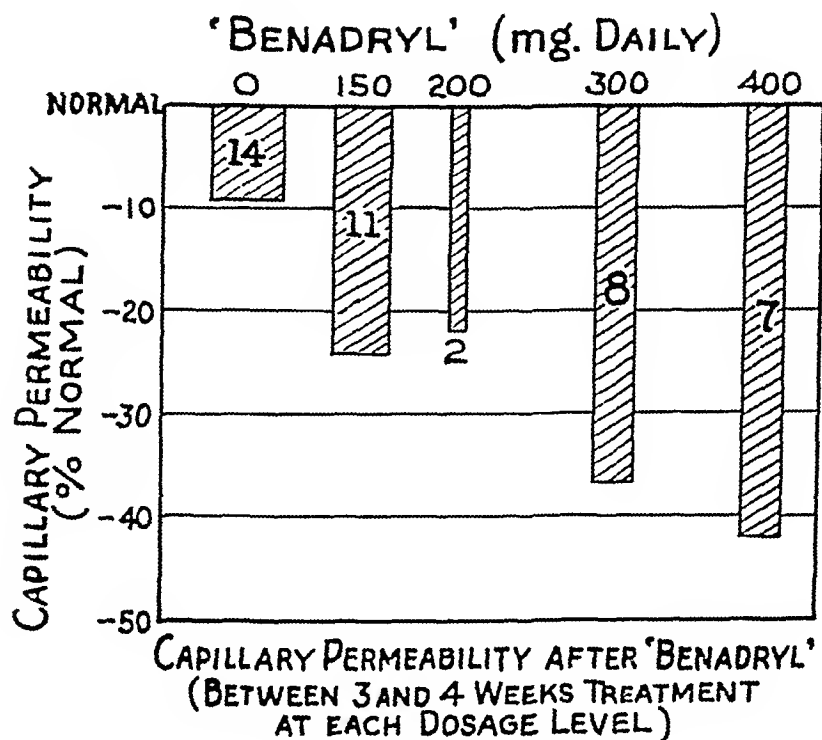


Fig. 3. Figures on the columns represent the number of subjects at the given level of dosage.

In view of the disturbance in accommodation brought about by "Benadryl," it seems fair to conclude that its action upon the eye following topical application simulates that of the alkaloids of the belladonna group.

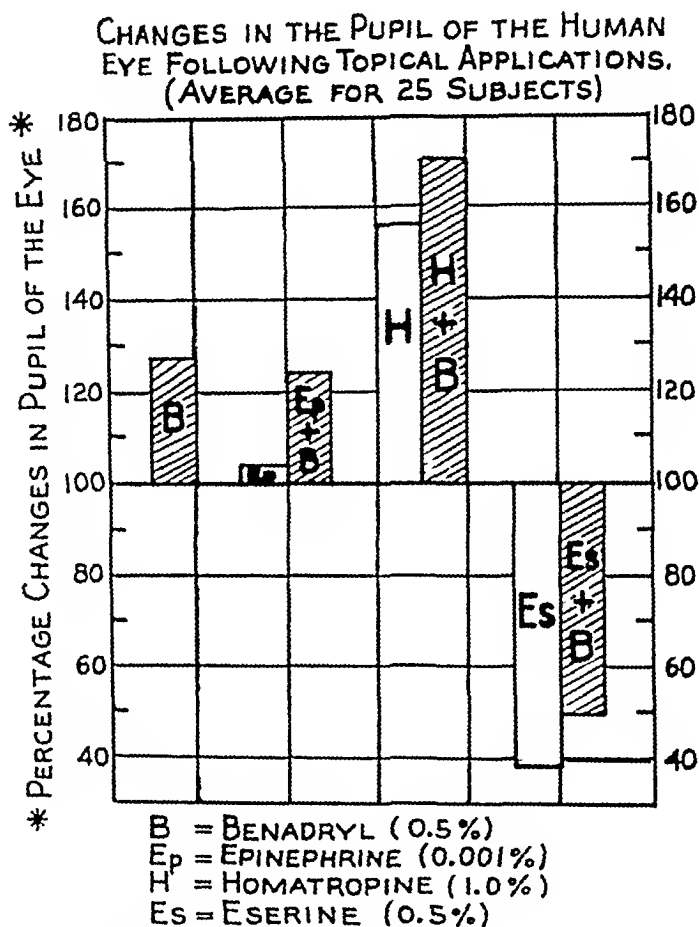
3. *Less Well Understood Pharmacologic Effects of "Benadryl."* The influence of "Benadryl" upon the central nervous system will be discussed under toxic reactions. Nevertheless, it seems important

ability was decreased in the majority of instances when 300 or more milligrams of drug were administered daily.⁴

The systolic blood pressure was lowered by 10 mm. or more of mercury in 29 of 74 patients ingesting from 250 to 600 mg. of the drug daily over periods ranging from 21 to 280 days (Table 2). Five of these subjects (6.8 %) developed an orthostatic hypotension (Table 2) which was completely asymptomatic in 4. Following a

single dose of 400 mg. of "Benadryl" orally to 14 subjects, a tendency to lowering of the blood pressure, sometimes maintained for several days, was observed. Orthostatic hypotension occurred in 5, as illustrated in patient S. M. (Fig. 5). It seems difficult to consider these actions as atropine-like, unless we concede the point that the more toxic effects of atro-

pine were simulated.⁵⁴ Neither do they seem to be an antagonism to acetylcholine, which in itself has a lowering effect upon blood pressure. A vaso-dilatation of blood vessels has been reported in the ears of rabbits following the use of "Benadryl".⁴⁵ In view of the fact that the size of the capillaries does not seem to have been altered, it would then appear that the



* The "fore" measurement is arbitrarily accepted as 100% in terms of which all subsequent readings are calculated.

FIG. 4.

TABLE 2.—BLOOD PRESSURE CHANGES IN 74 PATIENTS TREATED WITH "BENADRYL"

	No. Pts.	Dose				Treatment (Days)	
		Range	Aver.	Range	Aver.	Range	Aver.
No Change*	15	150-600	254	2.2-145.0	15.2	14-311	61
Lowering*	29	250-600	289	5.0-138.0	23.8	21-280	68
Orthostatic Hypotension	5	200-400	360	8.4-34.8	17.1	21-90	57

* A variation of 10 points or less from the original figure was ignored. No value was classified as lowered unless repeated pressures at frequent intervals were consistent.

variations in blood pressure may have been due to a prearteriolar or small blood-vessel vasodilation.

(b) Action on glucose tolerance. Intravenous glucose tolerance tests were performed upon 14 subjects under standard conditions already detailed.⁴² No change in tolerance could be elicited when a single 400 milligram dose of "Benadryl" was given orally $\frac{1}{2}$ hour prior to the beginning of the test. When 20 mg. was given intravenously there was a definite increase in tolerance shown by an average decrease of 69 mg. per 100 cc. in the level for blood sugar $\frac{1}{2}$ hour after the infusion was begun. The total area of these curves for the 4 hour period was 30.1%, less than the area of the control curves in the same subjects. Moreover, as compared with curves concomitantly made on 3 additional subjects these variations were statistically significant.⁴³

A priori we had more or less expected either no change or a decrease in tolerance in these tests. The reason for the increase observed is not entirely clear. It could be related to a phasic interaction between the drug and the autonomic nervous system, and through the latter to the influence upon pancreas or liver, or both.

Therapeutic Experiences With "Benadryl." Dimethylaminoethyl benzhydryl ether hydrochloride has been used successfully in the treatment of etiologically diversified cases of urticaria, angioneurotic edema, and pruritus;^{2 7 8 11 32 33 34 35 36} and in the management of physical allergies.^{39 43 51 62} Results have been satisfactory but much less dramatic in the majority of patients with hay fever^{21 23 26 37 37} and vasomotor rhinitis.³⁷ A much smaller percentage of patients with bronchial asthma have obtained relief.^{21 23 37 41} In all, we have observed 242 patients with a wide variety of complaints while under treatment with "Benadryl" (Tables 3 A, B, C, D, and E). In view of our knowledge of the antihistamine action of the drug, these cases may be logically divided into several groups:

A. DISEASE AFFECTING THE SKIN, IN WHICH HISTAMINE IS BELIEVED TO PLAY A PATHOGENIC ROLE. The drug has been tested in the conditions for which sudden and prolonged release of histamine are believed to have a pathogenic relationship.

All of 18 patients with *angioneurotic edema* (Table 3A) were improved by daily doses of "Benadryl" ranging from 150 to 300 mg., and total doses varying from 750 to 15,150 mg. Of the 5 patients designated as "improved" in the table, 3 had complete relief of the edema but not of an associated urticaria. A fourth was relieved of the edema, but was unable to tolerate the drug, even 100 mg. daily in divided dose; on the 5th day after it was stopped the edema recurred. The fifth patient had only 5 days of treatment at the 150 mg. dosage level for a chronically recurring condition. It would appear that well over 90% of the patients with angioneurotic edema can be quickly controlled by a single large dose of the drug, and that recurrence can be prevented by daily doses of from 100 to 150 mg.

All four of the cases of generalized *pruritus* were improved, one completely — a middle aged man in whom the cause of the condition was never discovered. The other patients suffered respectively from senile pruritus, the pruritus of Fox-Fordyce's disease, and pruritus secondary to an emotional upset. The itching in the case of the girl with Fox-Fordyce's disease has been controlled for 5 months with a dose of 250 mg. daily, but there has been little or no recession in the characteristic lesions of the disease.

Of 36 patients with *acute and chronic generalized urticarias*, 26 were completely relieved, 7 showed improvement and 3 were not helped by daily doses of "Benadryl" ranging from 100 to 600 mg. over periods of time varying from 1 to 131 days. Two of these patients were sensitive to the injection of insulin, and doses of 100 mg. daily have been sufficient to keep them completely free of symptoms; the 131 day period of treatment refers to

TABLE 3-A.—RESULTS OF TREATMENT WITH "BENADRYL" IN 242 PATIENTS.
A. DISEASES AFFECTING THE SKIN.

Condition	Total No Cases	C R *	I *	Results No Relief	
				No.	%
Angio-neurotic Edema	18	13	5	0	0.0
Generalized Pruritus	4	1	3	0	0.0
Urticaria	36	26	7	3	8.3
Allergic Eczema	6	1	2	3	50.0
Neuro-dermatitis	9	1	2	6	66.7
Total	73	42	19	12	16.4

* C. R.—Complete Relief. I.—Improved.

TABLE 3-B.—RESULTS OF TREATMENT WITH "BENADRYL" IN 242 PATIENTS
B. DISEASES OF KNOWN ALLERGIC ETIOLOGY ((EXCLUDING SKIN).

Condition	Total No Cases	C R *	I *	Results No Relief	
				No.	%
Bronchial Asthma	36	18	12	6	16.7
(a) Intrinsic	12	9	2	1
(b) Extrinsic	7	2	3	2
(c) Mixed	17	7	7	3
Hay Fever	8	5	1	2	25.0
Vasomotor Rhinitis	11	7	1	3	27.2
Allergic Hydrarthrosis	1	1	0	0	0.0
Total	56	31	14	11	19.6

* C. R.—Complete Relief. I.—Improved.

TABLE 3-C.—RESULTS OF TREATMENT WITH "BENADRYL" IN 242 PATIENTS. C. DISEASES IN WHICH
AN ALLERGIC ELEMENT MAY BE PRESENT.

Condition	Total No Cases	C R *	I *	Results No Relief	
				No.	%
Functional Dysmenorrhea	9	6	2	1	11.1
Spastic colon	15	7	4	4	26.7
Other G. I. Neurosis	10	1	5	4	40.0
Migraine	17	7	5	5	30.0
(a) Vaso-constrictor	6	2	2	2	
(b) Vaso-dilator	8	3	2	3	
(c) Not classified	3	3	0	0	
Ménière's Syndrome	5	1	2	2	40.0
Total	56	22	18	16	28.5

* C. R.—Complete Relief. I.—Improved.

TABLE 3-D.—RESULTS OF TREATMENT WITH "BENADRYL" IN 242 PATIENTS.
D. MISCELLANEOUS CONDITIONS.

Condition	Total No Cases	C R *	I *	Results No Relief	
				No.	%
Intractable Insomnia	9	3	2	4	44.4
Cardiac Asthma	8	1	3	4	50.0
Hypertension	8	0	2	6	75.0
"Degenerative" C. N. S.					
Lesions	19	0	4	15	78.9
Epilepsy	3	0	0	3	100.0
Heterogeneous Group	10	0	0	10	100.0
Total	57	4	11	42	78.9

* C. R.—Complete Relief. I.—Improved.

TABLE II. SUMMARY OF RESULTS OF TREATMENT WITH "BENADRYL" IN 212 PATIENTS

Group	Total No. Cases	CR*	Percentage		
			Improved	No Relief	%
A. Diseases of the Skin with an Allergic Component	74	12	19	12	16.4
B. Other Diseases of Known Allergic Etiology	76	11	14	11	14.6
C. Diseases in which an Allergic Element May be Present	70	22	31	16	28.6
D. Miscellaneous Conditions	57	1	1	12	78.9
Totals	277	46	62	51	
Per Cent	100.0	16.6	22.6	33.5	

* C R = Complete Relief; I = Improved

one of the insulin-sensitive individuals. In several of the acute conditions a single dose of 100 mg. served to give complete relief. Of the 3 patients listed as obtaining "no relief," one contracted a chronic urticarial condition over-ears in the African theatre of war, associated at times with a weeping eczematous eruption. A second patient with chronic urticaria of unknown etiology stopped the drug after taking 200 mg. daily for 3 days because of untoward reactions, although the lesions were improved. The third received the drug for a single day with improvement in itching but no objective change in the appearance of the lesions.

The causes of these urticarias included drugs, foods, and contactants; in some instances, psychic factors and sensitivity to bacteria within the respiratory passages were believed to excite the attacks. As soon as the condition was controlled by treatment, offending foods and drugs could be ingested without recurrence of the condition as long as the drug was continued and usually for several days thereafter. One patient with insulin sensitivity was treated continuously for 2 weeks since which time (3 months) she has needed no further medication to keep her symptom free despite the maintenance of her insulin regime.

Three of 6 patients with *allergic eczema* were not improved by "Benadryl." However, no daily dose of more than 200 mg. was tried in this group, and in two instances the alkamine ether was only continued for 3 days. In no instance had the condition been present less than 9 months, and in the one patient who com-

pletely recovered, it had lasted for 6 years (since birth) and disappeared after 4 days' treatment with 200 mg. daily; following 18 more days of treatment with 150 mg. daily, the patient has remained completely free of symptoms for 1 month.

Neurodermatitis was much more difficult to control than either of the conditions just mentioned. Two-thirds of the group were relieved but the time necessary for a satisfactory response varied from 17 to 60 days (except for 1 patient improved in 3 days) on daily dosages ranging from 150 to 100 mg. Historically and objectively there was nothing prior to treatment which distinguished the improved from the unimproved group.

B. DISEASE OF KNOWN ALLERGIC ETIOLOGY (EXCLUDING SKIN). Fifteen of the 36 patients with *asthma* were in status asthmaticus when treatment was begun. There were no consistent criteria by which those cases that did respond could be distinguished *a priori* from those that failed to do so. Our percentage of patients with bronchial asthma that obtained relief from "Benadryl" in the present series is considerably higher than that reported by other workers.^{15, 25, 26, 30, 37, 57, 63} If our interpretation of the literature is correct, we believe the apparent discrepancy lies in the mode of application of the drug, and the results which may be expected from its administration.

Attention to several simple rules may materially improve the results to be obtained by the use of the drug. Acute attacks may be prevented in many instances if from 2 to 4 capsules are taken with the advent of the very first symp-

toms. No dramatic response can be expected from any dosage level (up to 100 mg. every 4 hours tried) in the patient with status asthmaticus, or even in the individual whose attack, though not too prolonged, is well established before the drug is administered. In status asthmaticus, the first sign of improvement is usually seen by the end of the first 24 hours, and other substances, such as aminophyllin which had previously been ineffective, begin to evoke a response. Once the patient is free of the immediate attack, he should be placed upon a daily dosage level sufficient to ward off recurrence. As a rule 200 mg. daily, of which 100 mg. is given at bed time, will be sufficient to maintain the patient free of symptoms, although as much as 400 mg. daily with 150 mg. taken at bed time has been necessary. In addition an extra dose of 50 to 100 mg. is advised at the first warning of distress. One patient who has had daily nocturnal attacks for 3 years and diurnal distress three times weekly for 3 years, has been maintained completely free of discomfort during the past 4 months with a total daily dose of 400 mg. Moreover, he has not experienced any "side-effects" from so large a dose of "Benadryl". It is further clear, that patients who already have secondary changes in the lung and heart will not respond as satisfactorily as those who are free thereof. Whether or not the asthma is intrinsic, extrinsic or mixed seems to make very little difference in the response. In asthma and in other allergies where a long continued regime of treatment must be followed it may be necessary to increase the initially effective dose to maintain the same degree of response. Apparently a tolerance according to the principle of Le Chatellier-Braun is involved in this phenomenon.

About 75% of the patients with hay fever and vasomotor rhinitis have been relieved of their attacks with "Benadryl" (Table 3B). As a rule, these cases are quite readily controlled on small doses of the drug—from 100 to 150 mg. daily. Two

of the 5 recorded failures in these 2 groups were only treated for 2 days with a total dose of 300 mg. each. A third had an associated "widespread eczema" and "neuro-dermatitis." In the other two cases, the drug was discontinued because of "side reactions."

C. DISEASES IN WHICH AN ALLERGIC ELEMENT MAY BE PRESENT. Six of the 9 patients with a "functional" dysmenorrhea had been treated hormonally without success. Two of this group of patients had an associated spastic colon and 2 others a gastrointestinal neurosis with epigastric manifestations. All of these were relieved by "Benadryl". The 1 patient who obtained no relief from her dysmenorrhea with "Benadryl" had a thyrotoxic goitre with malignant exophthalmos. Four of 7 of these patients have been carried through 4 or more periods, and 3 additional patients through 2 cycles, while 2 have been watched during one. The necessary dosage, usually 200 mg. daily, was begun 3 or 4 days before the period was due. If there was any sign of pain, additional doses were added at 3-hour intervals.

While the role of histamine in the production of functional dysmenorrhea may be open to doubt, the association of such a condition with disturbances in the balance of the autonomic nervous system appears to have been accepted.^{5,19,20,22} The results certainly justify an extended trial.

Continued treatment was necessary to relieve patients with a *spastic colon*. The necessary daily dose rarely exceeded 200 mg.; 1 patient has remained comfortable after 8 months of treatment with 100 mg. daily, and has gained 15 pounds in that time. There was no apparent difference in the presenting manifestations of those patients who did and those who did not respond. The question of the role of histamine in the pathogenesis of spastic colon is perhaps a mooted one, but at least some of the evidence favors a positive relationship.^{3,45}

Other gastro-intestinal neuraxes, which were for the most part psychic in origin, were not materially improved by "Benadryl".

Some cases of *migraine* obtained dramatic relief from "Benadryl", either in a single dose of 100 mg. by mouth or from an intravenous injection of 20 mg. Whether the headache fell into the so called vasoconstrictor or vasodilator group seemed to make little difference in the result.

The 1 patient with *Ménière's syndrome* who obtained complete relief with "Benadryl" was symptom free 20 minutes after a single oral dose of 50 mg. and remained without attacks for 2 months by the daily use of a similar dose. This was the only 1 of the 5 patients in which a true, or so-called idiopathic type of *Ménière's syndrome* was believed to exist. Two of the others were on a hypertensive basis and the remainder were thought to be secondary to arteriosclerosis.

D. MISCELLANEOUS CONDITIONS. Because of the drowsiness so frequently experienced following the administration of "Benadryl", 9 patients with insomnia who were chronically habituated to the derivatives of barbituric acid were given "Benadryl" at bed time in doses ranging from 100 to 300 mg. Two of the 4 patients whose sleep was not improved had arteriosclerotic heart disease with some degree of chronic left ventricular failure. A third slept satisfactorily following the use of 3 capsules (150 mg.) nightly, but was "woozy" and fatigued all of the next day. In those patients whose sleep was satisfactory, there was a tendency for a decreasing effect as the drug was continued, so that one patient ceased to obtain relief by the end of the second week despite increasing doses, and all but one have had to increase the dose materially. If the drug was used discontinuously, the effects were much better maintained. The relationship of these findings to the drowsiness experienced by other patients who need the drug for the treatment of allergy is obvious.

Attempt was made to improve the status of patients with a *cardiac asthma*. The spastic wheezing asthmatic respiration of these individuals was routinely improved with large doses (between 400 and 600 mg. daily in divided dose). Inasmuch as 50% of the individual showed improvement its further trial in this condition appears to be warranted, and the presence of a histamine release factor in severe forms of left ventricle failure is suggested.

Because "Benadryl" has produced a reduction in blood pressure in many subjects (Table 2) a therapeutic trial was made in 6 cases of essential *hypertension* and in 2 with arteriosclerosis and hypertension. Neither of the latter were helped. The blood pressures of each of the remainder were lowered but the clinical condition improved strikingly only in 2; in 1 of these the changes initially observed justified the classification of a malignant phase of essential hypertension. In this patient, after 8 months of treatment with daily doses of 300 mg., blood pressure is normal, no new lesions have developed in the eyes, and previous symptoms have disappeared. No attempt should be made to evaluate these findings until a large series of patients has been observed over a relatively long period of time.

Of the patients with "*degenerative lesions of the central nervous system*", 4 had multiple sclerosis, 4 paralysis agitans, 3 progressive muscular dystrophy, 3 spinal muscular atrophy, 5 a long since inactive *tuberculosis dorsalis*. In view of the drowsiness, dizziness, and at times incoordination produced by "Benadryl", and the congestion of the choroid plexus observed in animals intoxicated with it, it seemed justifiable to test its usefulness in some of the conditions of the nervous system associated with lesions in and around the thalamus and basal ganglia. Three of the 4 patients with paralysis agitans, all of an arteriosclerotic type, believed they experienced subjective improvement as a result of the long continued use of the drug. A change in tremor and work performance, observed in two of these who received the drug for

relatively long periods of time (for 5 and 15 months, respectively), was not entirely accounted for on a psychic basis. One patient with multiple sclerosis has also been listed as improved although a purely psychic response in his case is not ruled out. There was no change in the status of any of the other 19 patients in this group.

In view of the sedative effect of "Benadryl" in some instances, it was tried in 3 patients with *idiopathic epilepsy* of the grand mal type. In each instance a very definite aggravation of status was observed. It is difficult to interpret such a finding, but it may perhaps be related to blood vessel tonus and to altered capillary permeability.

ity. Despite the ability of "Benadryl" to dilate blood-vessels⁴⁵ the intermittent claudication of an arteriosclerotic individual was not relieved. It is possible that pruritus ani may respond to the local application of "Benadryl" but one instance of this condition was not relieved by its oral ingestion in doses of 600 mg. daily for 3 days.

The Nature and Frequency of Toxic Reactions to "Benadryl". In order of their frequency, drowsiness, dryness of the mouth, dizziness, weakness and fatigability, incoordination and lightheadedness, and blurring of vision were encountered commonly as untoward reactions associated with the oral administration of "Benadryl" (Table 4). In conjunction

TABLE 4.—UNTOWARD REACTIONS IN 242 PATIENTS RECEIVING "BENADRYL"*

Condition	Number and Per cent of Reactions Observed on Daily Dose of (mg.)†						Total Reactions
	50	100	150	200	300	400 or more	
Number of Patients on Each Dose‡	28	20	135	79	74	44	...
Sleepiness	5 (18)	3 (15)	55 (40)	21 (26)	11 (15)	10 (22)	105
Dryness of the Mouth	1 (3)	0	28 (20)	5 (6)	8 (10)	6 (13)	67
Dizziness	0	0	28 (20)	12 (15)	5 (6)	9 (20)	54
Weakness and Easy Fatigability	1 (3)	1 (5)	19 (14)	4 (5)	5 (6)	6 (13)	36
Incoordination and Lightheadedness	1 (3)	1 (5)	6 (4)	1 (1)	0	2 (5)	11
Blurring of Vision	0	1 (5)	5 (3)	3 (4)	0	1 (2)	10
Totals	8	6	141	79	47	44	283

* 131 of the 242 showed some one or more unpleasant symptoms following the administration of "Benadryl".

† When "reactions" occurred in any given individual at more than one dosage level, they are recorded separately for each; hence, the apparent discrepancy between the total number of patients in whom untoward symptoms were observed and the total number of such symptoms.

‡ Figures in parenthesis represent the approximate percentage of subjects affected at the given level of dosage

In the "heterogenous group" of patients were included one with duodenal ulcer, one with cirrhosis of the liver, one with Sudek's atrophy, 3 with thyrotoxicosis, 2 with cardiospasm, one with generalized arteriosclerosis, and intermittent claudication, and one with pruritus ani. None of these were improved. It had been hoped that the tremor of hyperthyroidism might be relieved. No atropine-like action could be observed in the cases of cardiospasm. The patient with duodenal ulcer gave no evidence of clinical improvement despite a marked decrease in gastric acid-

with the incoordination and lightheadedness, thickness of speech and impairment of memory were often seen. The blurring of vision was not entirely due to the disturbances of accommodation to which reference has already been made.

Manifestations which occurred and which may have been directly due to the action of the drug included headache, nausea, anorexia, "butterflies in the stomach", "all-goneness at the pit of the stomach", "restlessness of the legs", "buckling at the knees", excessive perspiration,

faintness, intolerance to noise, and ringing in the ears.

In all, 131 of 242 patients developed some unpleasant symptom. The highest percentage of reactions was observed in patients who received 150 mg. of "Benadryl" daily. In many of these the symptoms disappeared while the drug was continued at the same dosage level. The mildness of these distressing symptoms is further emphasized by the fact that they necessitated stopping "Benadryl" in but 5 instances. In 3 of these, a feeling of extreme fatigue associated with an "all-gone sensation" at the pit of the stomach was more distressing than the allergic condition for which relief was obtained. In a fourth subject, sleepiness due to the drug was more incapacitating than her asthma. In the fifth patient, a case of spastic colon, dizziness, nervousness, fatigue, dryness of the mouth and some incoordination all occurred at levels of dosage (250 mg. daily) necessary to control her symptoms, and were so severe that she refused further medication at any dosage level.

Each of the symptoms recorded in Table 4 has been seen at every dosage level used. Drowsiness was by far the most easily evoked, and often a single dose of 50 mg. necessitated the use of caffeine or other similar stimulant to keep the subject awake during the 2 to 3 hours immediately following its administration. None of the other symptoms has been incapacitating until daily doses of 300 or more milligrams were used, or when a single oral dose of 400 mg. was administered.

Tolerance for the drug improves rapidly as its administration is continued. In 69.4% of the patients noting untoward symptoms while taking 150 mg. daily, these were improved by the end of the third day and had disappeared completely within 10 days despite the continued use of the drug. In 28.1% the dose was reduced with disappearance of unpleasant symptoms and was later increased to its former level and beyond without recurrence. In 2.5% the drug could not be

used at any dosage level without distressing manifestations. If the drug was stopped for 10 days or longer, the resumption of its use might again be associated, although not necessarily, with the originally experienced side effects, to which tolerance could again be acquired.

A decrease in the unpleasant effects produced by "Benadryl" was occasionally associated with a decrease in the effectiveness of its action against the condition for which it was being administered therapeutically. An increase in dosage usually overcame this problem and was rarely associated with a recurrence of the "toxic" manifestations for which tolerance had been acquired.

The exact nature of many of these toxic symptoms is not clear. The combination of drowsiness, dizziness, lightheadedness, thickness of speech, slight incoordination of movements, and impairment of vision are quite suggestive of a hyoscine-like action. Even the lowering of blood pressure seen with the larger doses utilized for prolonged periods of time may be similarly interpreted.

The Question of Dosage. How much "Benadryl" shall we give and how long shall we use it? The practical considerations of the two points raised in this question hinge upon the fact that "Benadryl" blocks the action of histamine in a quantitative manner and is utilized in the process. Therefore, the matter of dosage becomes a highly individualistic one, varying from patient to patient and often in the same patient from time to time. For any one of the conditions in which the drug has been found useful, we have employed successfully as little as a single capsule (50 mg.) daily in some instances, and in others have needed as much as 600 mg. daily. Above the latter dosage we have not tried the drug. There is certainly no rule of thumb which covers all cases. However, experiences to date afford us a few general principles.

1. All ambulatory patients should begin treatment with 50 mg. three times daily. If well tolerated the dose may be rapidly

increased—even doubled or trebled—with-
in 24 to 48 hours.

2. The first dose of drug should be given at a time when the patient will not be called upon to perform skilled movements depending upon acts of judgment, for should he prove to be sensitive to the drug, irresistible drowsiness, or perhaps dizziness or blurring of vision may materially interfere with his activity, or even endanger his life. If this dose causes no distress, the patient need have little fear of subsequent disturbances, except in the rarest instance.

3. If the drug has been discontinued a considerable length of time, dosage should be resumed as though the patient had never previously received it.

4. Some diseases appear to respond more readily and at lower dosage levels than do others, although it cannot be overemphasized that each patient must be thoroughly individualized in this regard. In a general way, however, we have been successful with smaller doses (around 150 mg. daily) in such conditions as hay fever, hyperesthetic rhinitis, and Ménière's syndrome. The greatest extremes of dosage have been necessary in such conditions as angioneurotic edema, generalized pruritus, urticaria, allergic eczema, spastic colon, and migraine—varying from 50 to 600 mg. daily. Larger to largest doses have always been necessary to control bronchial asthma, neurodermatitis, functional dysmenorrhea, intractable insomnia and cardiac asthma, none of these responding readily below a dosage level of 200 mg. daily, and the majority demanding the continued use of 300 to 400 mg. daily. Indeed, it is now our rule to start patients with bronchial or cardiac asthma on 600 mg. daily, usually reducing to 400 mg. daily after 24 hours. However, we have maintained the initial dose for 1 week without ill effects. Four hundred mg. has been administered daily for as much as 160 days, during which time the patient has been completely free of attacks formerly occurring every night and usually at some time during every day; a lesser dose was

ineffective. In connection with asthma, it should be stressed that the nature of "Benadryl" activity does not adapt it well to the *immediate* control of an already fully developed acute attack. It will prevent an attack, and it will gradually bring status asthmaticus fully under control. In other words, it cuts off the supply of available reactive histamine, but is relatively ineffective against the tissue responses already initiated by that substance.

Intractable insomnia usually responds best to a single large dose of the drug at bed time. Usually 100 mg. is sufficient; occasionally, 150 mg. will be required. Sometimes the latter dose is followed by a "hangover" the next day.

5. The duration of treatment with "Benadryl" appears to be limited only by the requirements of the treated individual. We have given 400 mg. daily for more than 200 days without any subjective or objective evidences of untoward reaction. Patients with chronic dermatologic conditions, hyperesthetic rhinitis, chronic bronchial and cardiac asthma may all demand prolonged courses of treatment.

6. The beneficial influence of "Benadryl" may last for considerable periods of time after the drug has been discontinued, even though the total period of treatment was short. One patient with hyperesthetic rhinitis of 15 years' duration with nearly continuous symptoms has been free of any attacks for 6 months following one week of treatment with 100 mg. daily. A child of 9 years with allergic eczema dating from the first year of life received 2 weeks' treatment with 150 mg. daily. There was no recurrence for 3 months. Following a second similar course of treatment, there has been no recurrence for 6 months.

We have dwelt somewhat at length upon the question of dosage, for it is apparent that many failures to obtain best results from the drug have been predicated upon the hesitancy of the physician to vary the amount given. No "rule of thumb" dosage chart seems advisable in the present state of our

knowledge. The nature of the disease and the individual reaction both play a part in determining the optimum dose in each individual instance.

Summary. 1. Sixty normal subjects and some of 212 patients have been subjected to extensive clinical study while receiving dimethylaminoethyl benzhydrol ether hydrochloride ("Benadryl"). Among the positive effects observed were:

(a) Suppression of the dermal response to histamine in all of 27 individuals studied.

(b) A depression of gastric acidity in 20 of 21 subjects for whom such analysis was made.

(c) An atropine-like action upon the eye in 43 of 60 subjects following the topical application of the drug in a 0.5% solution.

(d) A lowering of blood pressure of more than 10 mm. of mercury in 29 of 71 patients when large doses of the drug were used; and orthostatic hypotension in five of these subjects.

(e) An increase in glucose tolerance following the intravenous administration of a single dose of 20 mg. "Benadryl"; and no change in tolerance following a unit dose of 400 mg. orally.

2. Two hundred forty-two patients have received "Benadryl" over periods of time varying from 1 day to 15 months. More than 90% of all patients with angioneurotic edema, generalized pruritus, urticaria, and allergic hydrarthrosis were relieved. Over 80% of all patients with bronchial asthma and functional dysmenorrhea were improved. Between 50 and 80% of all patients with allergic eczema, vasomotor rhinitis, hay fever, spastic colon, other gastro-intestinal neuroses, migraine, Ménière's syndrome, intractable insomnia and cardiac asthma were materially helped. Other conditions in which the drug was tried included neurodermatitis, hypertension, degenerative lesions of the central nervous system, epilepsy, duodenal ulcer, cirrhosis of the liver, Sudek's atrophy, cardiospasm, intermittent claudication, thyrotoxicosis and pruritus ani.

3. Effective dosages of "Benadryl" ranged from 50 to 600 mg. daily. Initial clinical responses usually followed within 20 minutes after the first dose, but were often delayed, as for instance in bronchial asthma, for from 12 to 30 hours. Maintenance doses have varied from 50 to 400 mg. daily.

4. Untoward side effects of "Benadryl" have been observed with unit doses of 50 mg., but may not occur with single doses as large as 400 mg. nor with daily doses of 600 mg. continued for periods up to 16 weeks. These "toxic" manifestations included, in the order of their frequency of occurrence, drowsiness, dryness of the mouth, dizziness, weakness and easy fatigability, incoordination and lightheadedness and blurring of vision. Uncommonly seen were headache, nausea, anorexia, all-goneness at the pit of the stomach, buckling at the knees, restlessness of the legs, excessive perspiration, faintness, intolerance of noise, and ringing in the ears. A tolerance is usually built up quickly against these unpleasant symptoms. In the majority of instances this occurs so rapidly that the dosage of drug used at the time of their occurrence does not need to be altered.

Conclusions. "Benadryl" is an alkamine ether with a powerful antihistamine action. This is clearly indicated by its ability to suppress completely the dermal and gastric responses to histamine, and to decrease capillary permeability. These effects are further demonstrated through the clinical relief afforded patients suffering with diseases in which sudden and/or prolonged releases of excessive quantities of histamine play a pathogenetic role.

An atropine-like activity for "Benadryl" is suggested by its effects upon the eye when applied topically. The variations in blood-pressure may simulate one phase of the action of atropine.

Disturbances in the sensorium observed in some of the patients receiving the drug have suggested a hyosine-like action. Moreover, the cardiovascular manifesta-

tions of the drug are compatible with the known influence of hyoscine in one phase of its action.

From the clinicians' point of view, "Benadryl" is an exceedingly potent antihistamine and antispasmodic drug which

lacks unpleasant cardiovascular and nervous side effects attendant upon the use of sympathomimetic agents such as epinephrine, ephedrine and benzedrin. Toxic reactions, while common, rarely preclude its continued use.

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THE INTRAVENOUS USE OF HUMAN ASCITIC FLUID IN SHOCK, NEPHROSIS AND ALLIED CONDITIONS

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IN 1938, Davis and White¹ utilized human ascitic fluid successfully as "a substitute for blood in experimental secondary shock induced by graded bleeding," at the same time observing the "absence of any deleterious effect in their experimental animals." A few months later, Choisser and Ramsey² reported similar success in primary shock. Working along this line, one of us (H.S.) et al.³ conducted experiments to verify such reports, and in 1940 reported equally encouraging results in the management of histamine shock in dogs, all of which survived, "the blood pressure rising above the shock level and back to the initial level even one hour after the cessation of the treatment, without any apparent deleterious effect." In human clinics, however, the use of human ascitic fluid has been very limited, as Barr⁴ remarked that same year. Under the circumstances we shall here describe, during the Japanese occupation of the Philippines, these few studies made on this subject, however, turned inspiring enough for us to dare try it in actual human cases and enjoy the privilege of observing its good results. The cases herein reported are, to date, the first of their kind in the Philippines. It is, therefore, mainly to incite more interest towards the proper appraisal of this therapeutic measure that we report these few cases in view of the very encouraging results we observed.

CASE 1. Our Trial Case. Our trial case was a male Filipino, of middle adult age, admitted into the medical service as a case of portal cirrhosis. Ascitis and edema of the legs were marked. Repeated injections of salyrgan gave temporary relief, as the

diuresis that followed each injection eliminated a great portion of the edema. However, both the ascites and edema of the legs reappeared days after the mercurial injections. The ascitic fluid was a transudate.

We then tried injecting into the patient his own ascitic fluid. Being our first case, the amount injected was only 5 cc., with our attention focused more on the possible untoward effects rather than the probable therapeutic results. The patient was watched continuously for the next 24 hours, particularly for cardiovascular developments.

Fortunately, no untoward result whatsoever was noticed, not even a mild febrile reaction. The injection was, thus, later repeated, until the single dose reached 20 cc. In all, no serious ill effects were observed. We repeat, however, that our main purpose in this trial case was to see any possible untoward effects. We did not then entertain its therapeutic potentialities in portal cirrhosis. Rather, these trials were inspired by our search for a possible substitute for other parenteral fluids, as whole blood, plasma, Ringer's solution and others, which, however ideal, were evidently disappearing from our armamentarium during those occupation days.

It must be mentioned how cases of hypoproteinemia were on the up-trend during those days, as a natural result of food scarcity. From these cases easily developed varying states of shock, especially when severe diarrhea and vomiting precipitated its rapid onset after the intake of some "spoiled food," indicating how frantic the struggle for existence then. From our trial case, therefore, we not only obtained our first clinical observations but also served as our first source of ascitic fluid.

CASE 2. Portal Cirrhosis Developing Collapse after Sudden Perforation of Peptic Ulcer. C. F., a 60 year old male Filipino, was admitted into the medical service on February 15, 1944, because of generalized abdominal enlargement and epigastric pain.

Evidences of the portal cirrhosis were the ascites and edema of the legs; the bromsulphalein test which gave a retention of 18% in the half hour specimen and about 10% at the hour. The ascitic fluid was a transudate, with nine grams per liter of protein. The blood NPN was 25 mgm. per 100 cc. The urine voided was around 500 cc. in 24 hours.

The existence of peptic ulcer was also supported by the history of recurrent attacks of epigastric pain for 3 years then, especially so when hungry and relieved by food, alkali and hot water bag application.

On February 28, he developed melena. The next day, acute abdomen became evident, with the blood pressure dropping to 90/65 mm. Hg. and the pulse rate going up to 130 per minute. Fluoroscopy revealed pneumoperitoneum. The case was immediately operated upon, revealing a perforated peptic ulcer. Hypodermoclysis of 400 cc. of Nor. Salt Sol. was given, simultaneous with venoclysis of ascitic fluid amounting to more than 100 cc. given during the operation. No untoward results were observed. The patient continued in the surgical service a whole week after the operation, with the peripheral circulatory failure never completely controlled. No second venoclysis was given as no more fluid was then available. In fact, no other fluid could be obtained for intravenous administration. With hypodermoclysis and circulatory stimulants, the patient's struggle finally gave way. It can, however, be definitely stated that the ascitic fluid given during the operation proved to be innocuous.

CASE 3. Nephrotic Syndrome. In this third case, we tested the use of ascitic fluid as a possible diuretic and remedy in hypoproteinemia of nephrotic nature, considering the relatively higher protein content of the ascitic fluid and its possible use as a substitute for other recommended fluids, as acacia solution and lyophile serum, both of which were evidently out of reach during those days.

J. T., a 12 year old male Filipino, came to the service on April 22, 1944, with abdominal

enlargement and swelling of the lower extremities. The present attack of edema was the second in a period of 4 months.

The diagnosis of nephrotic syndrome was supported by the marked anasarca, the normal blood pressure of 101/90 mm. Hg., the hypoproteinemia of 5.1 gm. %, and the inverted albumin globulin ratio of 1:1.40. Furthermore, there was pleural effusion in the right thorax. The urine exhibited marked albuminuria, with 1+ granular casts, 1+ pus cells and 2+ red cells.

On further study of the etiology of the syndrome, the abnormal equilibrium between the intravascular and extravascular fluids became our main concern. For immediate relief, paracentesis abdominis was performed, collecting a liter and a half of clear ascitic fluid.

Then on May 4, sterile human ascitic fluid, obtained from a cirrhotic patient, was given intravenously. The patient complained of some tightness of the chest, as we reached the 100 cc. level. So, further administration was suspended. We noticed that the injection was going on quite rapidly, and it was to this that we later ascribed the slight untoward effects. At noon time, he developed some chills and headache, and the temperature rose up to 38.9° C. One half cc. of 1:10,000 adrenalin solution was immediately given hypodermically. In the same afternoon, everything subsided. The remarkable results, however, more than made us surprised as the following days the patient began to eliminate large amounts of urine. From a 24-hour output of from 200 to 300 cc. before the injection, he urinated up to 2.5 liters daily, with a consequent drop of body weight from 37 kilos to 25 in less than 5 days. The diuresis continued at more than a liter of urine in 24 hours even after that immediate response, which thus prevented the reproduction of the former anasarctic state.

On May 16, a second intravenous injection was given, this time with only 20 cc., done so purposely to test whether with smaller amounts diuresis could also be obtained. The record, however, shows no further increase in urinary output, although the output maintained itself at the same pace of more than a liter. No untoward effect was observed in this second injection, as it was then given very slowly. To evaluate the results better, all other diuretics, such as

potassium acetate, were suspended days before the first intravenous injection of ascitic fluid. Even the fluid intake was controlled, to avoid any possible effect from an increase of extraneous fluids.

On June 3, the patient was allowed to go home, with practically no edema, except for some puffiness of the eyelids early in the morning, with the body weight at 25 kilos, and still with a daily output of more than a liter of urine.

This illness was closely associated to the taking of some "cassava" a few hours previous to the onset of the whole syndrome. No fever nor tenesmus was noticed by the patient. The stools were at first hard, but soon became soft, loose and finally completely watery. Collapse set in within three hours of almost continuous bowel movements.

The temperature was 35.4° C., the pulse imperceptible, the heart sounds practically

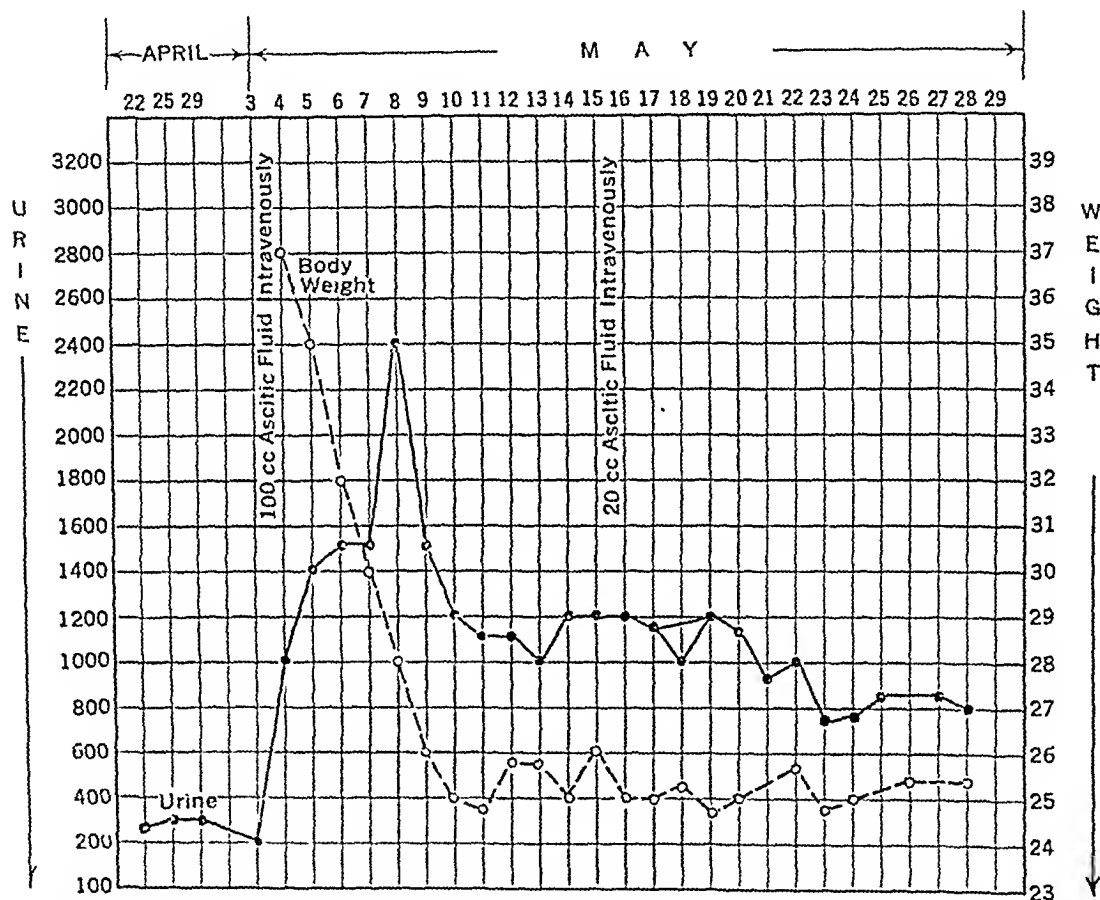


FIG. 1.—Nephrotic Syndrome. 24 hour urine output and body weight curves before and after intravenous injection of ascitic fluid.

CASE 4. *Case of Shock After Severe Diarrhea and Vomiting, Probably Due to Food Poisoning.* It was in this fourth case that we really met the condition for which we originally intended the ascitic fluid. The case was one of severe shock, rapidly developing after intense diarrhea and repeated vomiting due probably to food intoxication.

F. R., male, Filipino, 40 years old, was brought as an emergency case at 8:50 A.M. of Sept. 13, 1944, in a state of collapse. The trouble started the previous night as abdominal pain, followed by diarrhea and vomiting.

inaudible, the blood pressure unrecordable, the eyeballs sunken, and the skin with cold clammy sweats. Marked paleness was evident. Consciousness, however, was still present, the patient complaining of muscle cramps, especially of the calf muscles. *Laboratory reports:* 5,150,000 red blood cells and 11,500 leucocytes with practically normal differential count. The stools presented no macrophages nor parasites, with few leucocytes and completely watery in consistency.

He was treated with blankets and hot

water bags to the extremities; circulatory stimulants; and hypodermoclysis of 500 cc. of N.S.S. were given as initial measures. Then 500 cc. of sterile human ascitic fluid was administered by slow intravenous injection. No untoward effect was noticed during and after the injection. At 1:25 P.M. of that same day, the pulse became perceptible

ascitic fluid was then given at 5:00 of that same afternoon.

The next morning, the patient was evidently already out of danger. At 8:00, his temperature was 36.1° C., the pulse already full, with a rate of 100 per minute, restlessness subsided and the facies revealed the onset of convalescence. At 10:00 A.M., the

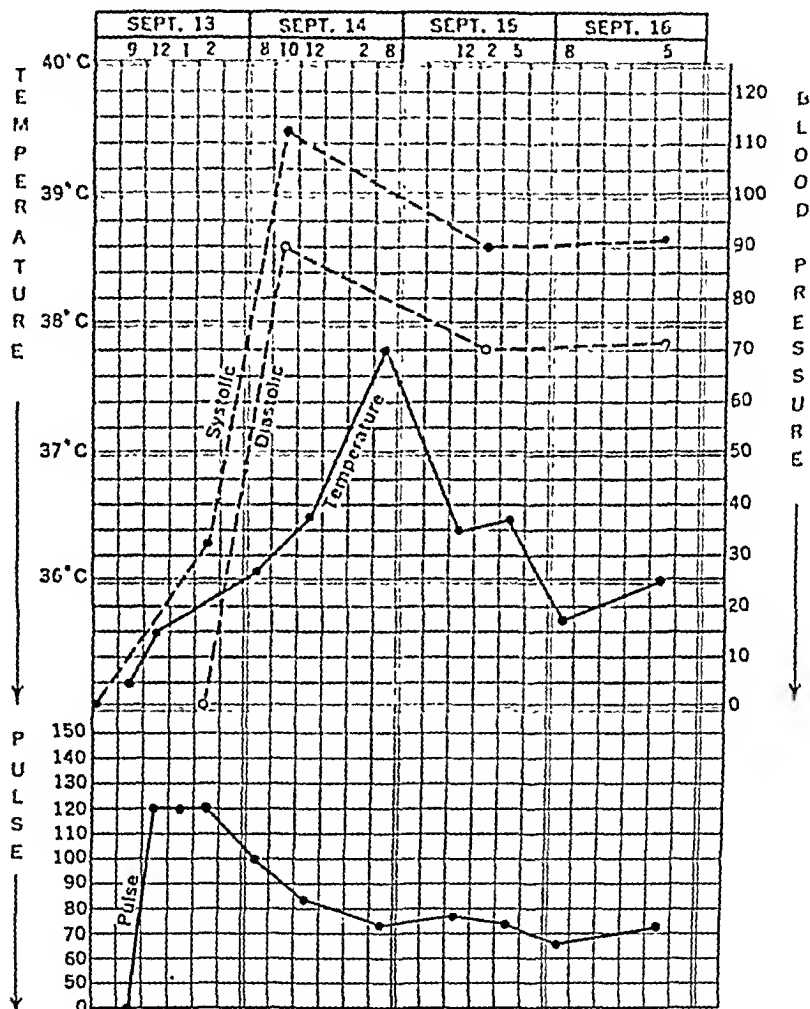


FIG. 2.—Shock, due to food poisoning.

for the first time since the onset of the collapse, with a rate of 120 per minute, though still weak and easily collapsible. Temperature was 35.6° C. The blood pressure was still undetectable. At 2:00 P.M., the sphygmomanometer finally registered a systolic reading of 32 mm. Hg. Another intravenous dose of 500 cc. of

blood pressure reached already 112 systolic and 90 diastolic; and at noon, his temperature reached 37.8° C. with the pulse rate of 75 per minute. All medications were then stopped, and only food and rest were prescribed. Two days later, he left the hospital completely cured.

OTHER CASES. *Two Cases of Shock After Perforation of Peptic Ulcer.* After the above mentioned cases, 2 other cases received intravenous injections of human ascitic fluid. They were cases of shock, following perforation of peptic ulcers.

The ascitic fluid was given as emergency measure, administered intravenously during the surgical operation. The amounts given varied, according to the available supply of ascitic fluid. However, no less than 50 cc. was given in each case. These 2 cases unfortunately succumbed a few days after operation, due to various conditions. We can safely state, however, that no untoward effect was noticed during and immediately after the intravenous administration of the ascitic fluid, nor can it therefore be the possible cause of the fatal outcome. On the contrary, it could be even asserted that it contributed its own towards the survival of these patients from the immediate dangers of both the operation itself as well as the collapsed state with which they went to the operating room.

CRITERIA AND PRECAUTIONS OBSERVED. Cognizant of the possible untoward and even fatal effects of this procedure, we observed strict precautions in the selection of ascitic fluids. The only kinds of fluids suitable for such intravenous use are those having the character of transudates; exudates being absolutely contraindicated even if these were apparently sterile. We obtained the fluids following the routine procedures for an aseptic operation, collecting it into sterile bottles. In this regard, some workers recommend the use of citrate. In our cases, we did not feel this to be very necessary, inasmuch as, after all, these fluids do not tend to coagulate spontaneously. Our sources were cirrhotic cases, cardiac cases, hypoproteinemic cases, both from undernutrition as well as of nephrotic nature.

A small sample was collected into a separate container for complete laboratory analysis. A simple Rivalta test sometimes was not sufficient, in view of false reactions for exudate even if the fluid was a real

transudate. This was particularly true in those in which the fluid had been in the body cavity for a sufficient length of time, allowing a good proportion of the water to be absorbed and leaving a good percentage of proteins in a relatively small liquid, thus sufficient to give reactions for exudate by the method of Rivalta. Such fluids would have been discarded if not further studied. And, these are precisely the kind of fluids which serve best our purpose, in intravenous injection—transudates with high protein content.

Total proteins were determined by either Esbach's simple technic or by the more elaborate procedures for total proteins in the blood. Then, cell counts and bacteriological studies were made. Needless to say, fluids yielding positive cultures, especially for spore-forming bacteria, were immediately discarded. On the other hand, a total cell count of 10 per cu. mm. was taken as the standard for transudate fluids.

Then, after it had passed the above criteria, the fluid was finally filtered through a Seitz filter into sterile containers and then heated in a water bath at 60° C. for 2 hours for 3 consecutive days. Thus, the fluid becomes ready then for either homologous or heterologous intravenous transfusion. If not readily used, it could be kept at refrigerator temperature preferably not above 12° C.

Comments and Summary. We repeat, these trials in human cases are the first of their kind in the Philippines. It was only because of the peculiarly unusual predicament in which we found ourselves during those three years of Japanese occupation that we felt courageous enough to resort to this measure in human cases, as a possible last remedy, in the absence of other fluids that are more highly recommended for parenteral use.

Fortunately, not only did we verify the few successful results that we were then aware of, not on experimental animals this time but in human patients, but also we realized the fact that ascitic fluid for intra-

venous use seems to have its rightful place in our medical armamentarium.

In all our cases, except in Case 3, no untoward effects were observed. Even in this case, the slight unpleasant side effects could easily be explained by the rapidity of its administration, an impression that was later verified in the next doses given more carefully and at a slower rate. The fatal outcome of the other cases operated upon, likewise, could not be ascribed to the venoclysis of ascitic fluid during the operations, as those patients survived the operations and succumbed several days later to varied conditions.

In Case 3, the unusual beneficial effects of ascitic fluid in nephrotic syndrome was evidenced by the marked, immediate and prolonged diuresis that ensued. A possible explanation could be the increase in the osmotic pressure in the blood, due to the higher protein content of the ascitic

fluid, similar to that said to be produced by the use of nearcia solution or lyophile serum in such cases of hypoproteinemia.

In cases of shock, as typified by Case 4, ascitic fluid could serve as a safe and efficient substitute for other parenteral fluids, and could thus be a life saving measure.

It is clear, therefore, that the use of human ascitic fluid intravenously is a safe procedure, provided that proper criteria are followed in the selection of the suitable fluids and certain precautions observed in its use. From the therapeutic results we observed in the cases here reported, we believe this subject merits consideration and further investigation. After all, one of the tendencies of recent advances and discoveries is the detection of the therapeutic potentialities of the very same products or by-products of the human body.

The junior authors of this paper offer this humble work as a tribute to the senior author, Dr. Ricardo Molina, whom we lost during the battle for the liberation of Manila. His guidance and inspiring courage have been the encouraging spirit that enabled us to undertake these trying experiences. Acknowledgment is also made to Dr. E. Medina Cue, Chief of the U.S.T. Clinical Laboratory, who was solely responsible for the selection, laboratory analysis and preparation of the ascitic fluids that we used in our cases.

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RENAL EXCRETORY FUNCTION AND DIET IN DIABETES INSIPIDUS

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THE primary dysfunction in diabetes insipidus is a deficiency in the supply of the antidiuretic hormone of the posterior pituitary gland, resulting in deficient reabsorption of water by the distal renal tubules⁵⁰ and thereby producing polyuria and polydypsia. In the diabetes insipidus of the dog, Winter, Ingram and Eaton⁵¹ have shown that the polyuria varies directly with the total daily osmimillimolar* excretion of NaCl and nitrogen (calculated as urea) of the urine. In man, likewise, these two constituents form the bulk of the various solids of the urine both in the normal⁵⁴ and in the diabetic insipidus patient²⁰; accordingly, a similar simple quantitative relationship might conceivably exist in the human also. This investigation was undertaken in order to clarify this point by a study of the renal excretory function of human diabetes insipidus. For this purpose data were utilized both from our patient and from eight other cases culled from a review of the literature on diabetes insipidus.^{3,20,30,43,46}

METHODS. Our patient was placed on a succession of measured diets, all equicaloric (about 2800 Calories) and varying in a calculated manner with regard to salt and/or protein. This patient as well as those of the other authors were allowed water ad libitum throughout all dietary regimes. The daily urines were collected from 7 A. M. to 7 A. M., the patient eating breakfast shortly after that hour. Total urine chloride was performed by the method of McLean and Selling⁵⁶ (expressed as grams of NaCl per liter) and total urine nitrogen by the micro-Kjeldahl method. In the calculation of milliequivalents of nitrogen in the urine, all the nitrogen was assumed to be in the form of urea,† following the method of Winter et al.⁵¹ This method of calculation of nitro-

gen excretion was followed also in recalculating the results of the other authors. In the conversion of milliequivalents to osmimillimols, no change was necessary in the case of nitrogen; the value of salt in milliequivalents was simply multiplied by two.

The cases of the other authors had had similar studies performed with diets varying in each patient both as to salt and protein intake so as to provide a range of daily excretion of nitrogen and salt from 200 to 700 osmimillimols. The urine specimens had been studied in essentially the same way.

PLAN OF STUDY. Our patient was placed on dietary regimes for five successive periods as noted in Table 1. The salt supplement to the diet was administered dissolved in fruit juice. In order to achieve an arbitrary total of 140 gm. of protein a day most conveniently, supplements of gelatin powder (Knox gelatin: 80% Protein) were administered in fruit juice. On the last day of period 5 (all periods were four days in length), the patient experienced anorexia, so that a small portion of the diet was not ingested.

The 8 patients of the other authors had similarly been placed on diets varying in protein and salt content, but not in the same calculated succession. These patients were either on a single type of regime for longer periods of time or simply on high or low salt or protein days. They all had in common however a number of days with sufficiently wide variations in total daily osmimillimolar excretion of urinary producers.

Results. Three characteristic deviations from normal renal function, observed in isolated cases previously,^{30,45} are here (Table 2) delineated more quantitatively: A. *The Low Average Urine Concentration;*

* Osmimillimols = $2 \times$ millimols NaCl + millimols urea.

† This method introduced a small error, particularly at low protein diets where the proportion of the nitrogenous excretion products of higher molecular weight is increased.^{13,34-5}

B. The Low Maximum Urine Concentration; C. The Low Reserve Urine Concentrating Power. As a conclusive demonstration of the fixed characteristic of the urine of diabetes insipidus, the normal is seen to have 42 times greater range of concentrating power than these patients. These conclusions can be applied equally well to the nitrogen and salt concentrating powers separately. It may also be noted that all

Fig. 1 shows a typical example from the data* in 1 case. The renal excretion curve of each patient, individually characteristic both as to slope and position in relation to the coordinates of the graph, could therefore be described mathematically by the formula:

$$UV = UV_0 + S \cdot O_{sm}$$

where UV is the daily urine output in liters, S the slope of the curve and O_{sm} ,

TABLE 1.—DIETARY REGIMES FOR FIVE SUCCESSIVE PERIODS

Diet Period Number	Total Protein Intake Gm.	Food Protein Intake Gm.	Gelatin Protein Added Gm.	Total NaCl Intake Gm.	Food NaCl Intake Gm.	NaCl Added Gm.
I.	85	85	0	6.5	6.5	0
II.	31	31	0	6.5	1.2	4.3
III.	31	31	0	1.2	1.2	0
IV.	140	85	55	1.2	1.2	0
V.	140	85	55	16.5	6.5	10

TABLE 2.—VARIATIONS IN URINE CONCENTRATIONS AND VOLUME*

Component	Diabetic Insipidus Patients† Range	Average	Normal‡
Nitrogen (as urea)	Max. 29-66	46.9	875 (Chaussin ⁴)
	Min. 9-31	17.2	162 (Folin ¹⁵)
	Diff. 17.5-11.0	29.7	713
NaCl	Max. 21-175	65.9	745 (Chaussin)
	Min. 1.4-80.0	23.2	146 (Folin)
	Diff. 3.5-95.0	42.7	599
Total N plus NaCl	Max. 56.8-215.0	91.6	1250 (Chaussin)
	Min. 36-165§	72.3§	440 (Folin)
	Diff. 5-50	19.3	810
Urine Volume	Max. 5.5-17.5	10.8	
	Min. 1.6-6.2	3.6	
	Diff. 3.1-14.0	7.2	

Comparative table of urine volume and concentration characteristics of normal and 9 diabetic insipidus patients (including the recalculated data from 8 cases of other authors^{3,20,26,43,46}).

* The urine volume is expressed in liters, the remaining components as osmillimols per liter.

† The diabetic insipidus patients had been on diets varying considerably but only a few approached in severity the stress under which the maximum values for the normal had been obtained.

‡ The data for the normal human at maximal dietary stress were secured from Chaussin⁴ as a resultant of several experiments on one patient and at normal dietary stress from Folin¹⁵ as an average derived from 6 patients.

§ These concentrations were secured from Table 3 C. The figures for the range were based upon the values of the individual patients in each case, maximum, minimum and differences.

the urine concentrations were reduced uniformly to about the same low range without a gradual transition from the normal.

For all the 9 diabetic insipidus patients the relationship between daily urine volume and daily output of urea and NaCl in osmillimols could be expressed with sufficient accuracy by a straight line.

the total daily renal excretion of nitrogen (as urea) and NaCl in osmillimols. UV_0 is the intercept constant of the line with the UV axis. These constants are shown in Table 3.

As a consequence of the above formulation, 2 additional characteristics of the renal function in diabetes insipidus emerge:

* The relationship was not as smooth when calculated in terms of milliequivalents. Osmotically, nitrogen and salt are of equal importance in the usual range of diets and renal excretion.

D. The Increment of Urine Necessary to Excrete Each Additional Osmillimol of Salt or Urea is Constant and Characteristic for Each Patient ("S"); and E. In a Given Diabetic Insipidus Patient, the Urine Concentration Expressed as Osmillimols Per Liter Increases as the Total Osmillimolar Excretion Rate Increases; in Different

Patients, The Rate of Change in the Total Osmillimolar Excretion Rate is the Greater the Greater the UV_0 of the Given Patient. Inspection of the actual data of these cases confirmed the latter statement in that, as the patients changed from lower to higher daily total excretion rates, those patients with the greater UV_0 showed increasing

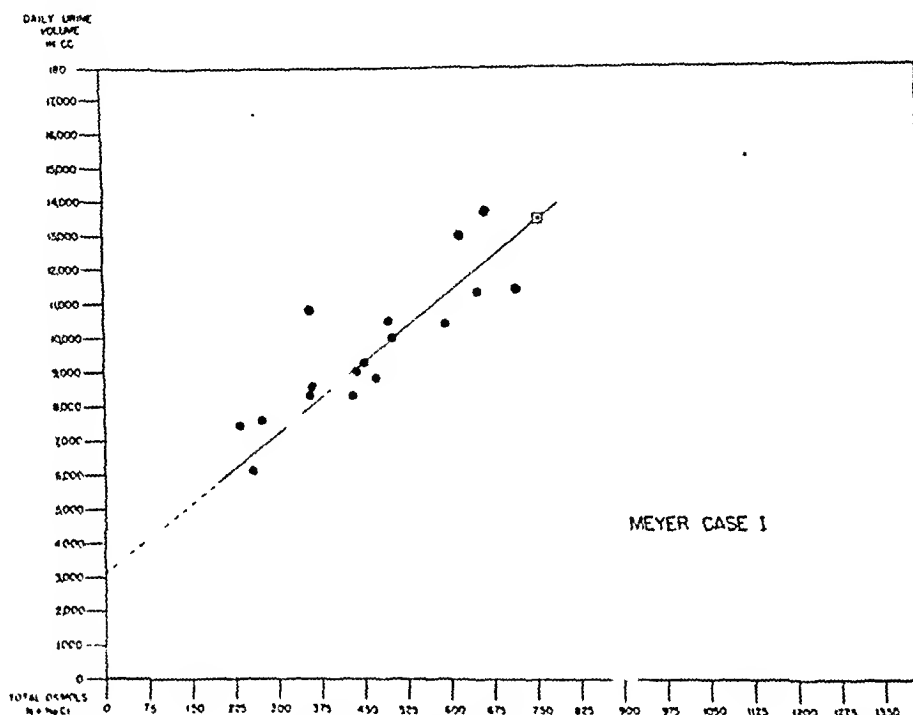


FIG. 1.—From a case of human diabetes insipidus (Meyer¹⁰ Case 1), data recalculated. The relationship between urine volume and total daily combined output of nitrogen and NaCl in osmillimols (labelled osmols) on varying diets. Square symbol represents output on unrestricted diet. The dotted line extension was an extrapolation. This curve was drawn by visual estimation. For constants according to the method of least squares, see Table 3.

TABLE 3.—EFFECT OF DIETARY RESTRICTION

Diet.		Meyer V	Allen IV	Beaser	Meyer II	Cases Tallqvist	Stenstrom	K&M	Meyer I	Allen III
A. Unrestricted	UV	5.5	8.0	10.5	10.5	10.0	11.5	7.5	13.5	10.5
B. Normal (Folin)	UV	2.7	6.7	7.3	5.2	7.0	9.7	6.6	9.3	12.2
	Osm.	440	440	440	440	440	440	440	440	440
C. Normal	UV	2.8	6.8	7.2	5.35	7.0	10.0	6.7	10.1	11.9
(calculated)	Osm.	462	510	434	462	443	462	462	498	427
D. Low Salt Ave.	UV	1.8	5.2	4.4	4.0	4.5	6.8	5.5	7.3	8.7
Protein	Osm.	284	332	256	284	265	284	284	310	249
E. Low Salt Low	UV	1.3	3.7	3.0	3.25	3.5	5.3	5.0	6.1	7.2
Protein Diet A	Osm.	196	222	181	196	190	196	196	209	175
F. Low Salt Low	UV	0.9	2.45	2.5	2.7	2.8	4.3	4.6	5.2	6.5
Protein Diet B	Osm.	139	139	139	139	139	139	139	139	139
G. Weight in Kgm.		72	90	61	72	65	72	72	81	60
H. Slope, S		0.0036	0.0122	0.0148	0.0074	0.0127	0.0154	0.0084	0.0128	0.015
I. Intercept, UV_0		1.61	1.18	1.04	2.16	1.02	2.50	2.94	3.78	4.48
J. Standard Error of UV		0.51	0.48	1.08	0.90	0.42	1.23	0.56	1.23	2.00
K. Maximum		± 1.0	0.78	1.9	2.12	0.8	2.1	1.3	2.8	4.8
Differences of UV		0.7	1.0	2.24	1.53	0.7	1.95	1.1	1.5	3.2

urine concentrations whereas those with low UV showed relatively constant urine concentrations.

As a further consequence of this formulation, we must revise our usual definition of severity in this disease, namely: the urine volume excreted on a regular diet. Instead, we may now estimate or calculate the severity of the diabetic insipidus renal function by the area beneath the patient's renal excretory curve or define its deviation from normal by the ratio between that area and that smaller area beneath the relatively constant normal human curve.

patient has been rearranged to illustrate the point that the greatest reduction of urine volume was attainable only when *both* dietary components were reduced to low levels* (protein, 1.49 grams per Kgm. body weight and salt, 1.2 grams per day).

In Table 3, this conclusion is confirmed for all the patients studied. The more moderately restricted diet (A) was able to reduce the urine volumes of 5 of the 9 patients to the relatively convenient zone below 3700 cubic centimeters. It is seen that the likelihood of ameliorating the polyuria by dietary restriction is the

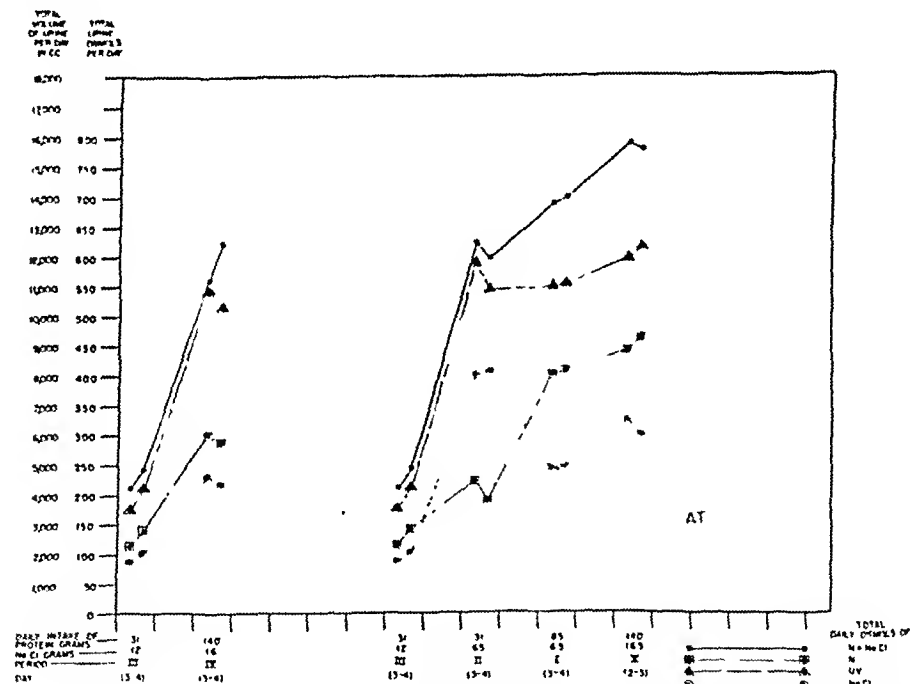


FIG. 2.—From our patient with diabetes insipidus. Data from the last two days of the diet periods of Table 1 rearranged to illustrate the effect upon urine volume and rate of excretion of salt and/or nitrogen, in osmolliters (labelled osmols), of variation in the quantity of dietary protein and salt, in that order.

No simple mathematical relationship could be observed between the *total* daily excretion of *either* nitrogen or salt and either diet or urine volume. However, the relationship between dietary intake and urinary output can now be seen with clarity. In Fig. 2, the data from our

greater the smaller the UV₀. Furthermore, it is of interest that the diabetic insipidus patients' desire for salt and protein when allowed a diet of choice cannot be relied upon to adjust itself to the concentration defect (unlike thirst). This is not related to the weight of the patients.

* That these conclusions were not due to the short duration of the diet periods was shown by the failure of a 15 day trial of a normal protein, low salt regime to reduce the urine volume to its lowest level.

Discussion. In defining more quantitatively the range of renal concentrating function in these patients with diabetes insipidus, it is worthy of note that all have been reduced to a relatively uniform low level, with none in the wide transitional area. In the light of the increasing evidence for the large reserve capacity of the antidiuretic mechanism of the posterior pituitary gland,^{33,37} this would seem to indicate that the disease represents practically complete decompensation of this mechanism. The importance of this concept is that it would classify the remaining excretory and concentrating characteristics of a given diabetic insipidus patient as largely residual and extra-pituitary in origin.

While the normal human evinces a slight tendency to constancy of urinary concentration on various diets,¹ this becomes pronounced when the kidney's concentrating powers are taxed.⁸ This invariability of urinary concentration in the diabetic insipidus patient then seems to be an exaggeration of a normal tendency of the kidney made obligatory by the low concentrating ability and low reserve, so that it works at practically its maximum (although low) rate at all times.

The straight line relationship observed between urine volume and osmotic output testifies to the exact correlation between water supply and requirements, since the diabetic insipidus patient cannot efficiently dispose of excess water as can the normal.³⁶ In view of the fact that thirst was the sole regulating mechanism of supply here, this further confirms the close interrelationship between thirst and osmotic balance of the body,¹⁶ represented here by osmotic excretory needs.

With the all or none concept of the pathogenesis of diabetes insipidus in mind, we may speculate regarding the signifi-

cance of the mathematical constants defining the renal excretory pattern of the individual patient. We might conceive of "S" as the basic distal tubular concentrating pattern of the patient, the individual characteristic features of which were brought to light only in the absence (or deficiency)* of distal tubular water reabsorption. The variable UV_0 which elevates the curve of the diabetic insipidus patient by comparison with the normal is equivalent to a constant excess of water requirement (thirst), independent of dietary load, and necessary to satisfy some set of circumstances associated with renal function and endogenous in origin. It probably is related to the other known renal abnormality of this disease, increased salt reabsorption by the proximal renal tubules.^{36,37} This, if continued, would tend to produce a more hypertonic blood (with respect to NaCl); the latter can be recognized as a most important physiological stimulus to increased thirst,¹⁶ in this case one which would be rather precisely geared (by a common origin) to the polyuria which it would be called upon to satisfy.†

The renal excretory curve may prove to be a useful tool for the study of this disease and the evaluation of therapeutic procedures; however, of immediate interest is the light it throws on dietary therapy. Efforts to control the polyuria by water deprivation accomplish little except dehydration and needless suffering.^{10,23,48} By contrast, it has been repeatedly observed that some restriction of dietary salt and protein has a beneficial effect.^{14,30,31,43,46} Some observers attained therapeutically incomplete results due to inadequate restriction of both constituents²⁰ or due to the curtailment of only one of them.²⁵ Allen, after a careful study, concluded that both had to be restricted radically to

* If, as some seem to assert,²² the diabetic insipidus patient has normal kidney excretory function but a pathologically increased thirst, he would have a curve of normal slope but elevated above the abscissa.³¹

† It is tempting to speculate that a variable portion of the increased salt reabsorption may be due to an unopposed adrenal cortical effect occurring as a release phenomenon in the absence or diminution of the effect of its antagonist, posterior pituitary gland. Under those circumstances, UV_0 should then be a function of the adrenal activity of the patient and should vary independently of the "S", as it does.

produce real benefit, that the effects were independent of caloric intake, and that patients could be so regulated for long periods of time with no deleterious effects.³ Because of unpredictable variation from patient to patient in the degree of therapeutic benefit attained,^{3,20} an understandable confusion ensued, resulting in the

necessary and that the degree of success attainable is both variable and predictable from the "S" and "UV₀". Moreover, the importance of reducing protein intake calculated on a weight basis would obviously be greater the heavier the patient. In the practical management of a given case, determination of the excretory curve

TABLE 4.—LOW SALT, LOW PROTEIN DIET (A)*

	Protein	Fat	Contents in Grams Carbohydrate	Salt
Breakfast:				
200 gms. Orange juice.	1	0	24	.016
15 gms. Dry cereal	1.5	0	7.5	.017
30 gms. Toast	2	0	16	.130
20 gms. Butter—salt free	0	16	0	.001
40 gms. Jelly—2 tablespoons	0	0	26	0.0
200 gms. Milk	6	8	10	.360
50 gms. Cream	1.5	10	2	.065
20 gms. Sugar—1 tablespoon	0	0	20	0.0
Dinner:				
45 gms. Roast beef, medium fat	12.1	8	0	.076
100 gms. Baked sweet potato	1.8	0	28	.060
100 gms. Asparagus	1.6	0	3	.060
100 gms. Sliced tomato	1.0	0	4	.060
30 gms. Mayonnaise—2 tablespoons	0	22.5	0	.128
30 gms. Bread	2	0	16	.130
20 gms. Butter—salt free	0	16	0	.001
40 gms. Jelly	0	0	26	0.0
100 gms. Banana	1.2	0	23	.206
50 gms. Cream	1.5	10	2	.065
20 gms. Sugar.	0	0	20	0.0
Supper:				
100 gms. Potato	2.0	0	19	.060
100 gms. Braised celery	1.3	0	4	.260
100 gms. Carrots	1.1	0	9	.050
100 gms. Lettuce	1.2	0	3	.120
30 gms. Mayonnaise	0.0	22.5	0	.128
100 gms. Cherries	1.1	0	15	.021
30 gms. Bread	2	0	16	.130
30 gms. Butter—salt free	0	20	0	.006
40 gms. Jelly	0	0	26	0.0
50 gms. Cream	1.5	10	2	.065
20 gms. Sugar	0	0	20	0.0
Totals:	43.4	143	341.5	2.221

General rules for a low salt diet: 1. All foods to be prepared without condiments. 2. No salt to be used at the table. 3. Use salt free butter. 4. Do not use commercially canned foods unless labeled salt free. 5. Avoid the use of foods of high salt content such as ham, pork, bacon, all nuts, salt water fish, and cheese.

* From Army Manual T. M. 8-500.

present day teachings which disregard or minimize the need for the reduction of the protein intake.^{4,7,9,32} Instead, the entire stress is laid upon replacement therapy which is now more easily administered than previously.^{6,17}

The present study has shown that restriction of both dietary constituents is

is an unnecessary refinement, for which can be substituted therapeutic trial of a diet. Diet A (Table 4) is attractive and convenient, while Diet B (Table 5), less appetizing but of greater potential benefit, satisfies the minimum human requirements.^{2,3,18,23,27,39,42,44}

The distribution as well as the total

amount of ingested food is of practical importance. In the diabetic insipidus as in the normal it is in the first several hours after a meal that the major portion of the nitrogen³⁰ and salt^{11,25,49} excretion of that meal occurs, in addition to a concomitant increase in the glomerular filtration rate.³⁸ In the normal human such excretion does not carry over into the

salt and protein and their redistribution to the breakfast and noon meals.

In order to draw general conclusions as to the applicability of dietary control in this disease, information regarding the frequency distribution of cases by severity would be desirable. The latter, based solely on urine volume on an unrestricted diet, can be estimated roughly from 2

TABLE 5.—LOW SALT, LOW PROTEIN DIET (B)*

	Protein	Contents in Fat	Grams Carbohydrate	Salt
Breakfast:				
200 gms. Orange juice	1	0	26	.01
30 gms. Dry cereal	2	0	24	.03
40 gms. Jelly	0	0	26	0.0
30 gms. Toast	2.5	0	16	.13
20 gms. Butter—salt free	0	16	0	.004
200 gms. Milk	6	8	10	.36
50 gms. Cream	1.5	10	2	.039
30 gms. Sugar	0	0	30	0.0
Ad Lib. Black coffee	0	0	0	0 0
Dinner:				
50 gms. Lamb chop	10	15	0	.15
100 gms. Carrots	1	0	9	.05
100 gms. Lettuce and tomato	1	0	3	.09
33 gms. Mayonnaise	0	25	0	.12
30 gms. Bread	2.5	0	16	.13
20 gms. Butter—salt free	0	16	0	.004
40 gms. Jelly	0	0	26	0.0
100 gms. Pineapple ice	0	0	27	0 0
50 gms. Cream	1.5	10	2	.039
30 gms. Sugar	0	0	30	0.0
Ad Lib. Black coffee	0	0	0	0 0
Supper:				
100 gms. String beans	1	0	3	.04
100 gms. Squash	0.5	0	4	.01
75 gms. Coleslaw	1	0	2	.03
33 gms. Mayonnaise	0	25	0	.12
30 gms. Bread	2.5	0	16	.13
20 gms. Butter—salt free	0	16	0	.004
40 gms. Jelly	0	0	26	0 0
100 gms. Grapefruit	0.5	0	10	.008
50 gms. Cream	1.5	10	2	.039
30 gms. Sugar	0	0	30	0 0
Totals:	36	151	340	1.537

(Total Calories: 2863)

* From Army Manual T. M. 8-500.

sleeping hours except when on excessive intakes, under which circumstances both salt⁸ and nitrogen^{24,38} excretion persist into the night, with accompanying nocturia. In the diabetic insipidus with a tendency to nocturnal polyuria on a normal diet, it would be highly expedient to avoid both the accumulative and immediate effects of diet by a total reduction of the intake of

large series of cases in the literature^{19,35} (Table 6). Of those patients, over 50% had an output of less than 8 liters per day. Since dietary regulation proved of great benefit even to the 8 patients (Table 3) with a daily urine output exceeding 8 liters, it would indicate a large sphere of usefulness for this type of treatment when used alone in diabetes insipidus.

With respect to replacement therapy, nasal pituitrin may be ineffective or only partially effective^{29,41} due to local absorption difficulties or to the severity of the disease. In either event, diet may be adequate to replace it entirely or to render it effective. Even inadequate dietary control such as salt restriction alone has been tried and found useful as an adjunct to the quick acting parenteral preparations.^{21,29} The newer slowly acting prepa-

Summary. 1. The low concentrating activity and reserve power of the diabetic insipidus kidney of man was quantitatively demonstrated.

2. A straight line relationship was noted between urine volume and the total excreted quantities of salt and nitrogen expressed in osmillinols.

3. This curve of renal excretion was found to be characteristic for each patient and was defined mathematically.

TABLE 6.—DISTRIBUTION OF CASES OF DIABETES INSIPIDUS ON THE BASIS OF "SEVERITY" *

Author	Below 8 Liters		Urine Volume 8-12 Liters		Over 12 Liters	
	Number	%	Number	%	Number	%
Rowntree ²³	19	31.5	21	38.2	15	27.3
Jones ¹⁹	31	76	5	10	6	14
Composite Total	50	51.5	26	27	21	21.5

* Severity in this table refers to the urine volume on an unrestricted diet.

rations, now being used more widely, have been most useful in the more severe cases, but carry with them the possibility of complications such as menorrhagia⁴⁷ or water intoxication.^{12,47} Here, too, diet would be of value both in ameliorating the polyuria and decreasing the dosage or frequency of administration of therapy. Certainly, dietary control is worthy of a trial in every case, with or without posterior pituitary extract, according to the severity of the disease.

4. A new quantitative definition of severity in this disease is proposed in terms of renal excretory dysfunction.

5. The renal excretory curve of a diabetic insipidus patient provides a quantitative method of measuring the effect to be expected from dietary restriction or other procedures.

6. It has been demonstrated that maximum restriction of both salt and protein of the diet is necessary in order to attain maximum therapeutic benefit.

The effect of dietary restriction upon urinary output of the 9 patients with diabetes insipidus. The values for urine output were derived from the excretion curves, the constants of which (H, I, J, K) were calculated by the method of least squares. Patients arranged in order, reading from left to right, of the lowest to the highest urine volumes attained at the lowest diet (F). Urine output, UV, was expressed as liters. Osm. indicates the osmillinols of nitrogen plus NaCl excreted at the eventually to be expected equilibria of the patients at the respective diets. Normal (Folin) diet was derived from Folin's "average" diet.¹⁵ Normal (calculated) diet was based upon 1.5 grams per Kg. of body weight of protein and 8 grams of salt daily.⁶ Low salt—low protein diets refer respectively to Tables 4 (low, definitely adequate daily protein)⁴⁰ and 5 (minimum, daily protein).³⁹ Where the author did not furnish the patient's weight, it was assumed to be 72 Kilograms.

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OBSERVATIONS ON THE TREATMENT OF CARCINOMA OF THE PROSTATE BY ORCHIDECTOMY

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THE treatment of advanced carcinoma of the prostate by androgen reduction through orchidectomy or the administration of estrogens as suggested by Huggins¹ has stimulated much discussion regarding the results to be achieved by this form of therapy. During the past 4 years the clinical as well as the endocrine and chemical aspects of such therapy have been energetically investigated. The following conclusions² are generally agreed upon: 1. Androgen reduction offers the best prospect for the relief of symptoms due to secondary deposits of prostatic carcinoma. 2. A significant number of patients are dramatically improved while many others obtain partial relief. 3. Some patients show little or no improvement, the downhill course of their disease being unaffected by any form of endocrine change.

At present, three methods of endocrine control are in use: Surgical castration, estrogen therapy, and a combination of these. There is as yet no unanimity of opinion regarding the exact indications for the use of any one of these methods. This is explained largely because there has not been sufficient time in which to observe and compare a sufficient number of patients treated by each method. Carcinoma of the prostate often runs a long and unpredictable course and this adds greatly to the difficulty of properly evaluating any type of treatment. An added difficulty is the lack of knowledge regarding the endocrine and metabolic changes brought about by these forms of therapy. Further evidence regarding the problem will depend, therefore, on endocrine studies

and continued clinical evaluation of patients treated by these methods.

In this report, we discuss the clinical findings of patients with carcinoma of the prostate treated exclusively by orchidectomy during the past 4 years. Additional surgical procedures for the relief of urinary symptoms were also carried out whenever necessary. Thirty-five patients have been studied and followed for from 6 months to 4 years, over half of them for more than 2 years. The patients varied in age from 53 to 87, the average being 70 years. Of the 35 cases, 20 had a positive microscopic diagnosis of carcinoma of the prostate, while in the remaining 15 cases the diagnosis was made by physical findings, elevated acid phosphatase, and Roentgen ray evidence of bony metastases. Of the 35 cases, 23 showed evidence of metastases either by Roentgen ray or acid phosphatase or both, while 12 had no evidence of metastases. Of the 23 with metastases, 9 died within one year after orchidectomy, two within 2 years and one 28 months after orchidectomy; 11 are living and relatively asymptomatic (8 to 25 months after operation). Of the 12 cases without evidence of metastases, 5 are living (6 to 30 months after operation), 3 died within the first year, one died in the second year, and 3 died after three years.

Thirty-one urologic operative procedures other than orchidectomy were performed in 22 of these cases. Cystotomy by suprapubic punch for the purpose of placing the bladder on constant drainage was done in 11 patients who were admitted

to the hospital in acute retention. Of this group one patient died of pneumonia after orchidectomy before any further procedure to free the bladder outlet could be carried out. Three patients were able to void after orchidectomy and the suprapubic opening could be dispensed with. One patient had a partial perineal prostatectomy to free the outlet of the bladder. The remaining 6 patients subsequently had transurethral resections.

Six patients had had a suprapubic prostatectomy prior to the development of carcinoma and 2 of these required further removal of tissue (transurethral resection) to free the outlet of the bladder. In 7 patients the prostate was explored through the perineum; one total and 3 partial prostatectomies were performed in 4 patients prior to orchidectomy, and 3 had a biopsy of the prostate through the perineum. Transurethral resection was carried out in a total of 10 cases. Three of these required a second transurethral resection at a later date. Suprapubic prostatectomy was carried out in 2 of the patients.

An analysis of the cases and the results of orchidectomy has been made from the following five aspects: 1. Relief of pain due to metastases; 2. Improvement in well-being (appetite, weight, etc.); 3. Roentgen ray changes in the metastases; 4. Improvement in urinary symptoms; 5. Changes in acid phosphatase.

1. Of the patients having metastases, approximately two-thirds experienced moderate to severe pain preoperatively. After removal of the testes dramatic and marked relief of pain was experienced by one half the patients and the other one-half showed slight to moderate improvement. No patient of the group with metastases failed to show some improvement, temporary though it may have been in some cases. In practically all of the cases surgical castration was followed by amelioration of symptoms within 48 hours. This rapid response suggests that pain as such is more likely due to pressure on or actual involvement of nerves by carcinoma

(usually in lymphatics or lymph nodes) rather than by intraosseous growth which will show no detectable change by Roentgen ray in so short a time. By way of illustration, the only case showing structural deformity of a vertebra due to carcinomatous invasion received only minimal relief from orchidectomy. One must assume that in this case pain was caused by vertebral collapse rather than by nerve involvement outside the spine. Little improvement, therefore, can be expected in cases in which the bony metastases destroy the normal contour of the vertebral column. On the other hand, where pain is caused by peripheral nerve involvement, one may expect relief in a majority of the cases.

Along with other observers⁸, we have found that patients who were bedridden and required large doses of opiates were able, in several instances, to resume their former occupations and no longer required sedation.

2. As might be expected, improvement in well-being and appetite paralleled relief of pain in almost all instances. There were also several cases, not suffering from pain and with no evident metastases, who showed an increase in weight, appetite, and general well-being. Improvement in well-being may be very rapid and dramatic as illustrated by the following case:

Case Report. CASE 1. The patient, a 65-year-old Italian longshoreman, entered the hospital in a very cachectic condition, having lost over 20 pounds in 6 months.⁹ He had suffered marked fatigability, anorexia, nausea, vomiting, and pain in the back and both legs. He had no urinary symptoms except slight nocturia.

Physical examination revealed a very pale, emaciated man who showed marked wasting of the extremities. There were no abdominal masses or lymphadenopathy. Rectal examination showed the prostate markedly enlarged with definite evidence of malignancy. Acid phosphatase determination was 12 units. Roentgen rays revealed osteoplastic metastases in practically every bone in the body, including the skull and ribs. A severe secondary anemia was also present.

Bilateral orchidectomy was performed and was followed by marked diminution in pain and cessation of nausea and vomiting within 48 hours. Acid phosphatase was 6 units on the eighth postoperative day. He was discharged much improved on the eleventh postoperative day. At the end of 6 months the patient had returned to limited work, had gained 22 pounds and his red blood count had become normal. At the end of one year he was feeling extremely well, was still gaining weight and his acid phosphatase was reduced to 1 unit. Fifteen months after orchidectomy he was readmitted to the hospital because of recurrence of severe pain in the back and both legs for two weeks. He also had pain in the right elbow and sternum. The patient had lost 10 pounds in weight and the acid phosphatase was re-elevated to 6 units. He was treated with large doses of stilbesterol—up to 5 mg. daily—but did not respond in any way, nor was there any relief of pain. His general condition became steadily worse and he died one month later.

This case further illustrates the symptomatic relapse which may occur at variable periods after orchidectomy. After relapse, these patients, as a rule, are little affected by therapy with estrogenic compounds and go rapidly downhill.

3. In our series of 35 cases, 18 had evidence of metastases as seen by Roentgen ray. Examination of the chest, spine and pelvis was carried out in each patient and other areas were examined whenever indicated. Osteoplastic metastases were observed in the spine and pelvis 18 times, ribs 9 times, pleura twice and lung fields twice. Repeated Roentgen ray examinations were possible in 16 of these patients at various intervals after bilateral orchidectomy.

An exact evaluation of the changes occurring in the Roentgen ray appearance of metastatic lesions is extremely difficult and requires that great care be taken both in the preparation and the interpretation of the films. They must be made under uniform conditions on repeated examinations in order to allow accurate comparison of the size, number and density of metastases. Careful comparison of both pre-

and post-operative films must always be made, particularly when it appears that new bony metastases have occurred since orchidectomy. Often review of the same areas in the preoperative film will disclose the presence of previously overlooked metastatic areas which have increased in density and thus first been noticed on the postoperative films.

In the bones there were no constant changes which could be interpreted as signifying regression. Most frequently the osteoplastic metastases became more calcified and appeared more discrete. A number of times, however, the lesions became larger as well as more numerous and widespread. In a few cases there was no significant change, and two cases only showed decreased density of the osteoplastic lesions with a partial restoration of normal bone architecture.

In one of these there was a remarkable diminution in the size of the metastases, almost all of the neoplastic areas being replaced by normal bone. This change had not occurred by one month after orchidectomy, but was noted on the second examination more than one year after operation. During this time the patient's clinical course has been extremely satisfactory. He has experienced complete relief from pain, has gained weight and has shown marked improvement in urinary function.

A very favorable change in the Roentgen ray appearance of metastases occurred in one of 2 patients having metastases to the lung fields. Three months after bilateral orchidectomy these secondary deposits were greatly diminished in size and the lungs appeared remarkably improved. The other patient showed a similar but much less striking change. Of the 2 patients with metastases to the pleura, one was unchanged after operation, and the other showed diminution in size of the metastatic nodules.

Several of the patients who showed a progression of metastases by Roentgen ray did so in spite of marked clinical improvement. One patient, previously free

of metastases by Roentgen ray, developed them throughout the spine and ribs three months postoperatively. He died shortly thereafter.

In general, it is our feeling that the Roentgen ray changes in bony metastases cannot be interpreted as indicating regression except in rare cases in which normal bone architecture is restored after orchidectomy. There is little in the usual Roentgen ray response to suggest the extent or duration of clinical improvement. However, in those cases in which there was partial restoration of normal bone architecture or clearing of metastases from the lung fields, there was also very satisfactory clinical improvement.⁴

4. There have been several reports in the literature stating that decrease in the size of the carcinomatous prostate and improvement of urinary function are to be expected following androgen depression therapy.^{1,3} It has been our experience that this favorable effect on urination cannot be expected in the majority of cases. Although a decrease in the size and softening of the original lesion was observed in about one-third of the patients treated, only 5 showed a resulting improvement of urinary function and diminished residual urine. Three of these had been placed on suprapubic drainage because of severe retention prior to orchidectomy, and in these the retention was relieved, permitting withdrawal of the catheter and complete healing of the suprapubic sinus. Two others showed a marked reduction in residual urine soon after orchidectomy. In all of these cases the prostate showed diminution in size and became softer.

A case in which local extension of the lesion showed diminution in size is of particular interest.

CASE 2. The patient, a 70-year-old expugilist, entered the hospital because of frequency, burning on urination, chills, fever, nausea, vomiting and pain in the left flank for one week. He had been treated at home with sulfathiazole, 3 gm. daily, since the onset of his illness without showing

any improvement. Four years previously at this hospital he had had a suprapubic prostatectomy for benign prostatic hypertrophy. At the present examination there were signs consistent with a blocked left kidney. The kidney was enlarged, tender, and showed no excretion on an intravenous urogram. Rectal examination revealed a markedly enlarged, stony-hard, nodular prostate with extension of malignancy into the seminal vesicles, particularly on the left side. The patient appeared acutely ill, had a high fever, and his urine contained many white cells and gave a heavy growth of *E. Coli* on culture. Acid phosphatase determination was 4.0 units. There was no evidence of metastases by Roentgen ray. Bilateral orchidectomy was performed and within 96 hours the clinical signs and symptoms produced by the blocked kidney disappeared and the urine became clear. Subsequent to this the patient has gained 20 pounds, is able to do light work around his farm and has remained well for 2 years. Shortly after orchidectomy several examinations showed that the prostate was definitely smaller in size, particularly in the region of the seminal vesicle on the left.

That the number of cases showing a decrease in size of the prostate and improvement of urinary function is small is not surprising when one considers that in many cases obstruction to urination is contributed to or wholly caused by benign prostatic hypertrophy, which so often occurs together with carcinoma of the prostate. One could, therefore, expect improvement of urinary symptoms only in those patients in whom the obstruction at the bladder outlet was largely due to malignant growth. It is our feeling that if urinary symptoms are severe enough to suggest the need for operative interference, this should be performed at the same time as orchidectomy rather than to wait for possible improvement from the latter procedure alone.

5. It has been repeatedly observed that the elevated serum acid phosphatase of patients with metastatic carcinoma of the prostate decreases following androgen depression therapy. The decline is most rapid during the first week after orchid-

ectomy, and thereafter a more gradual decrease occurs for the next 2 to 3 months. Of the 35 cases studied, 12 showed no clinical or Roentgen ray evidence of metastases and had a normal acid phosphatase, that is, 4 units* or less. Of the remaining 23 with metastases, 21 had acid phosphatase values above 4 units. All 21 cases displayed a reduction in acid phosphatase level after surgical castration, 12 of them ultimately returning to normal. In our experience this is of no prognostic significance, since a number of the patients whose acid phosphatase became normal and remained within normal limits succumbed within 3 to 10 months. On the other hand, in some cases a re-elevation of the acid phosphatase coincided with a clinical relapse and progression of metastatic involvement. The finding of a normal acid phosphatase in 2 of the cases with definite evidence of metastases by Roentgen ray is in keeping with the general experience of others. However, the serum acid phosphatase determination must be regarded as a valuable diagnostic aid, since a definitely elevated acid phosphatase (above 10 units) is almost never present in the absence of metastases.⁹

Discussion. Although the series reported is small, it is our feeling that the cases are varied enough to represent an adequate cross-section of the disease, its manifestations, and the results one may expect from orchidectomy as a method of treatment. Undeniably orchidectomy will prolong the life and comfort of a significant number of patients with metastases. In patients with advanced metastatic disease suffering severe pain and incapacitation, orchidectomy may result in dramatic improvement.

Unfortunately, there are few if any clinical or laboratory clues which enable one to foretell how any one patient will respond to surgical castration. However, the high percentage of immediately favor-

able results following this form of treatment makes its employment worthwhile in almost all cases.

The length of time during which a patient may be benefited by castration and remain free of pain varies considerably. The shortest period of improvement among our cases was 3 months, while the longest period of improvement to be followed by relapse lasted 24 months. As a rule the reappearance of pain was coincidental with rapid deterioration of the patient's general condition and was soon followed by death. In several such cases even large doses of stilbesterol failed to modify the downhill course of the patient or affect the pain.²

The question of the optimal time for orchidectomy has remained unanswered. Many authors advise withholding orchidectomy until metastases or symptoms thereof appear. Nesbit and Cummings,⁷ for instance, express the opinion that, "... the maximum benefit to the patient may be derived by delaying endocrine treatment until indicated by the onset of symptoms arising from advanced or metastatic lesions." Others believe that the general life expectancy may be prolonged if orchidectomy is performed early, regardless of the presence or absence of metastases. Higgins (as quoted by Meads⁶) and others hold to this view. The possible beneficial effect of the operation on the local lesion as well as the possibility of delaying the appearance of metastases favor this opinion. It has been our policy in most cases to perform orchidectomy whenever the diagnosis of carcinoma of the prostate is made, regardless of the presence or absence of metastases.

Summary. Thirty-five cases of carcinoma of the prostate treated by orchidectomy have been studied.

Of the 23 cases with metastases, 12 died within 28 months and 11 are living, the

* One unit is defined as the degree of phosphatase activity which at pH 4.9 and 37° C liberates from a specified citrate buffer monophenylphosphate substrate solution 1 mg. of phenol in 1 hour, by the Gutman modification of the King Armstrong method for "alkaline" phosphatase. The number of units is determined to express the amount of phosphatase activity in 100 cc of blood serum (9).

longest for 25 months after operation. Of 11 cases without metastases, 5 are living, the longest for 30 months after operation.

Marked relief was experienced by one-half of the patients with pain within 48 hours, and slight to moderate relief occurred in the others. Improvement in well-being and appetite paralleled relief of pain in almost all instances.

Following orchidectomy the bony metastases showed increased density and be-

came more discrete in the majority of instances, and sometimes also increased in size and number.

A decrease in size and softening of the original lesion was observed in a number of cases after operation, but improvement in urinary function attributable to orchidectomy alone occurred in only a few cases, and it was necessary to perform other operations to free the bladder outlet in 22 patients.

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THE FEMORAL BONE MARROW CELLS OF THE ALBINO RAT

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NUMEROUS careful morphological studies of the peripheral blood of the albino rat have been published. The data have been well summarized recently by Griffith and Farris.¹ The same authors have referred briefly to the bone marrow, which they have regarded as similar to that of man save for its "preponderantly erythroblastic, pronormoblastic and normoblastic" character. Only two previously reported detailed studies of the bone marrow in the normal rat have been found, (Stasney and Higgins,⁶ Toppner⁷). Additional information from a small group of control animals has been included in the reports of experiments on the effects of sulfanilamide (Higgins and Machella⁸).

Several difficulties are to be encountered in discussing the myelogram of man or of laboratory animals: (1) The variety of methods used by different investigators. (2) lack of uniformity in nomenclature and (3) failure to record the findings in a sharply defined manner. The present study is concerned with the development of a dependable method for obtaining data, the accurate description of cell types observed and a tabulation and classification of these.

Method. Twelve normal albino rats, of the Rockland strain, ranging in age from 6 to 8 months, were kept in the laboratory, from the time of birth, at a uniform temperature. They were fed exclusively on Rockland Farm Vitamin-D-free rat pellets (the standard diet used in our laboratory) and had free access to fresh water.

For obtaining each sample of bone marrow the animal was lightly anesthetized with ether. A dorsal incision was made parallel to the femur, the muscles were separated to expose the entire length of the bone, which was rapidly disarticulated and removed. During this procedure the

amount of anesthesia was increased so that the animal expired at, or shortly after, the time the femur was completely removed. The bone was immediately bisected with a jeweller's saw and all of the marrow was withdrawn by a syringe through a 20-gauge needle and transferred to the center of each of a series of drops of saline, on separate slides, with which it was thoroughly mixed by rotating the tip of the needle. The smear was made in the usual manner by drawing the drop across the slide with a second slide. Simultaneously smears of peripheral blood were obtained by snipping the tail. The slides were air-dried for 30 to 60 minutes and treated, in the majority of instances, with Jenner-Giensu stain. Wright's stain was used for at least one smear taken on each animal, and several of the total number of smears were stained with the Sato Peroxidase technique in order to identify cells of the myeloid series about which some doubt could be entertained. The differential count, in each instance, was based on the study of 1000 cells.

Results. I. CELL TYPES. Several types of cells were differentiated and classified. A description of each follows:

The "blast" cell is peroxidase-negative. It is round or slightly ovoid in shape and approximately 15-26 microns in diameter. It has a moderately dark, clear, blue cytoplasm. The nucleus is round and takes a light violet-colored stain. The darker-staining chromatin appears to form an over-all, fine, lacy or net-like structure. One to 5 small, well-defined nucleoli are invariably present: They take a lighter and bluer stain than the nuclear groundwork.

The promyelocyte is similar in size, shape and staining reactions to the "blast" cell. The nuclear chromatin, however, is ar-

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ranged in heavier strands, forming a mesh-like pattern. Nucleoli, similar in number and staining reactions to those in the latter cell, are present although they frequently are less clearly defined. A few dark purple or azurophilic granules are noted in the cytoplasm. They are usually separated from the nucleus by a distance of 2 to 4 microns.

The myelocyte is round or ovoid in shape. It has a diameter of 14 to 20 microns. The violet-staining nucleus may be round or oval. The chromatin is arranged in fairly large, shallow heaps, giving the nucleus an unevenly furrowed or shaded appearance. Nucleoli are absent. The cytoplasm contains a varying number of granules. These may be small and lavender, or large and reddish-orange in color. Occasionally azurophilic granules, reminiscent of previous development stages, are observed. The cytoplasm, as seen between the granules, assumes a grayish-blue or pinkish-lavender cast. The cells are recognized, on the basis of the size and color of the granules, as the progenitors of the neutrophilic and eosinophilic granulocytes.

The "ring" cell is similar in size and shape to the myelocyte. The nucleus is round or ovoid and stains a violet color. The chromatin is arranged in moderately heavy clumps and coarse strands. Located at or near the central part of the nucleus is a well-defined ring-shaped opening, giving the nucleus a "dough-nut" appearance. With both the Jenner-Giemsa and Wright stains this opening has either a lilac or pinkish-yellow color. Lavender granules and, occasionally, small azurophilic granules are present in the cytoplasm, which assumes a moderately light blue or grayish-blue cast.

The metamyelocyte is round or ovoid in shape and has a diameter of approximately 12 to 16 microns. The cytoplasm takes a light grayish-blue, lilac or pinkish-yellow stain, the blue cast tending to predominate. It contains numerous distinct, small lavender granules or large, reddish-orange granules (neutrophilic and eosino-

philic series, respectively). The nucleus, which is indented or kidney-shaped, is deep violet in color, with the chromatin concentrated in small, dense heaps and coarse interlacing strands. It is noted that the nucleus of the eosinophilic metamyelocyte takes a somewhat lighter stain than that of the neutrophilic metamyelocyte.

The staff cell (juvenile granulocyte, stab cell, rhabdocyte) is spherical in shape and approximately 10 to 16 microns in diameter. The cytoplasm is pinkish-yellow although the presence of lavender granules in the cells of the neutrophilic series tends to give it a lavender cast while the presence of orange granules in the cells of the eosinophilic tends to give the cytoplasm an orange-yellow cast. The nucleus of the cells of the former series stains a deeper violet than that of the cells of the latter series. The nucleus of the staff cell may be rod-shaped, curved in the form of a horseshoe or ring-shaped. There is no evidence of lobulation. The chromatin is arranged in coarse, interlacing strands.

The mature granulocyte is essentially like the staff cell in size, shape and cytoplasmic and nuclear staining reactions. The nucleus is lobulated. The lobulations, which are joined by fine, hair-like strands, range from 2 to 6 in number in the neutrophils and from 2 to 3 in the eosinophiles.

The mature *basophilic granulocyte* is similar in size and shape to the other mature granulocytes. It has a light blue cytoplasm and an irregularly shaped, pale violet nucleus, which occasionally has a somewhat lobulated appearance. The presence of large, deep-staining purple granules in the cytoplasm tends to obscure nuclear detail and outline.

The erythroblast is round or ovoid in shape and varies from 8 to 20 microns in diameter. The cytoplasm, compared with that of the cells of the myeloid series, has a definitely opaque, rather than a translucent, clear quality. It may vary in the intensity of basophilic staining from a moderately dark to a very deep blue or greenish-blue, or it may exhibit numerous

degrees of polychromatophilia. Hemoglobin may be present as is indicated by the occasional occurrence of orthochromicity. The nucleus usually occupies one-half to two-thirds the diameter of the cell. It is round in shape and stains an intense, dark, purplish blue. Numerous block-like masses of basichromatin appear sharply demarcated from surrounding areas of paler-staining oxychromatin. In the majority of polychromatic erythroblasts the arrangement of the chromatin tends to give the nucleus a cartwheel appearance. Occasionally the nucleus is lobulated or star-shaped, in which instances very little oxychromatin is discernible. The cell is frequently seen in the process of mitosis.

The *normoblast* is spherical and has a diameter of approximately 7 to 10 microns. The cytoplasm is orthochromatic or polychromatic, rarely basophilic. The nucleus is round and has the appearance of a homogeneous, blue-black mass. It varies considerably in size in relation to the total cell, frequently occupying so much of the cell volume that only a narrow rim of cytoplasm is visible. Normoblasts containing pyknotic nuclei are occasionally noted.

The *lymphocyte* is round or ovoid in shape, approximately 7 to 14 microns in diameter, and has a clear, very light blue cytoplasm which may contain a few, fine, scattered red granules. The nucleus occupies an eccentric position and varies in size, occupying one-quarter to three-quarters of the total cell volume. It may be round or slightly indented in shape and stains a violet color. The chromatin structure is relatively coarse, basichromatin occurring in clumps which merge gradually into lighter-staining areas of oxychromatin.

The *monocyte* is similar in size and shape to the larger lymphocyte. The cytoplasm takes a grayish-blue stain and contains very fine, scattered, reddish-purple granules, which give it a "dusty" appearance. The nucleus may take the shape of a thickened horseshoe or appear folded back upon itself. It stains a bluish-violet color,

somewhat lighter than that of the lymphocyte. The arrangement of the chromatin resembles that of the latter cell.

The *megakaryocyte* is a large, irregularly shaped cell, amoeboid in type. It varies from 25 to 40 microns in its widest diameter. The cytoplasm stains a pale lilac color which tends to fade toward the periphery; it contains minute azurophilic granules which may be densely aggregated in some areas. The nucleus is large and irregularly shaped or lobulated. Chromatin, staining a dark, bluish-violet, is concentrated so as to outline lobular borders; the balance of the chromatin is arranged in small clumps enmeshed in fine filaments.

The *macrophage*, or *reticulo-endothelial* cell is ovoid in shape and approximately 15 to 30 microns in diameter. The cytoplasm takes a moderately deep blue stain. The nucleus may be round or lobulated and stains a dark blue: it is not too well delineated for the entire cell tends to have a cloudy appearance. Frequently engulfed erythrocytes or leucocytes may be observed within the cell membrane.

The "*kugelhaufen*" is irregular in shape and varies in diameter from 15 to 24 microns. A minute amount of lavender-staining cytoplasm may be seen: this is obscured, to a great extent, by the presence of relatively large purplish-black particles, resembling bullets or pieces of coal. These particles tend to break through the cell membrane and scatter in the immediate vicinity of the cell. An eccentrically placed round or ovoid, pale lavender-staining nucleus is noted: this is traversed by numerous fine interlacing strands of violet-colored chromatin.

The *plasma cell* is ovoid in shape and approximately the size of the larger lymphocyte. The cytoplasm appears dense and opaque and takes a deeply basophilic stain except in the perinuclear area, which is relatively pale. Occasionally small vacuolated areas, resembling bubbles, are noted in the cytoplasm. The nucleus, which is round, is approximately one-third to one-half of the diameter of the cell:

it almost invariably occupies an eccentric position. Basichromatin, staining a very deep blue or bluish-purple color, is divided into relatively large blocks, sharply demarcated from the sparser oxychromatin, and is arranged in a cartwheel, or radiating manner.

as above described. In each instance, not less than 1000 cells were differentiated in a single specimen. The results are tabulated in Table 1.

Similar data for the peripheral blood of the rats studies are included in Table 2.

Each element of the blood of the rat

TABLE 1.—DIFFERENTIAL COUNT OF THE CELLS FOUND IN THE BONE MARROW OF TWELVE NORMAL ALBINO RATS (1000 CELLS)

Myeloid/Erythroid ratio—1.78 (average).

Cell Type	No. of cells per 1000 cells Range	Mode	Mode In	Number of rats Below	Above
Mature neutrophiles	168-281	230-245	6	4	2
Neutrophilic staff cells	76-220	110-150	6	4	2
Neutrophilic metamyelocytes	24-48	30-42	8	1	3
"Ring" cells	42-90	49-65	8	2	2
Neutrophilic myelocytes	16-40	20-30	5	3	4
Bromyelocytes	3-18	6-12	8	2	2
Mature eosinophiles	25-70	40-47	8	2	3
Eosinophilic staff cells	12-60	24-42	7	3	2
Eosinophilic metamyelocytes	6-19	6-13	7	3	2
Eosinophilic myelocytes	1-5	2-3	6	2	4
Mature basophiles	0-2	1	4	6	2
"Blast" cells	23-61	29-43	5	2	5
Erythroblasts	80-160	100-120	8	2	2
Normoblasts	188-300	220-240	8	2	2
Lymphocytes	18-53	25-45	7	2	3
Monocytes	0-6	2-4	9	2	1
Plasma cells	4-10	4-6	7	0	5
Megakaryocytes	0-16	1-3	8	3	1
Macrophages	0-4	1	8	2	2
"Kugelhäufen"	0-2	1	5	4	1

TABLE 2.—DIFFERENTIAL COUNT (100 CELLS) OF THE PERIPHERAL BLOOD OF TWELVE NORMAL ALBINO RATS

	Neutrophiles	Lymphocytes	Monocytes	Eosinophiles
Range (per cent)	16-38	53-81	0-3	1-12
Mode (per cent)	22-30	64-77	1	2-6
Rats in (No.)	6	7	2	6
Rats below (No.)	3	2	9	4
Rats above (No.)	3	3	1	2

The degenerated cell (basket cell, smudge cell) is one which has either degenerated due to senility or which, because of its fragility, has been broken in making the smear. It is irregular in outline, takes a uniform reddish-violet or bluish stain and shows a loss of nuclear and cytoplasmic structure. A small percentage of cells of this type are present in all smears. They cannot be identified with any certainty.

II. THE PERCENTAGE OF THE VARIOUS TYPES OF CELLS ENCOUNTERED IN THE FEMORAL BONE MARROW AND PERIPHERAL BLOOD OF THE RAT, RESPECTIVELY. Counts of the femoral bone marrow were made from diluted smears fixed and stained

showed a greater normal variation than the same element in the blood of the healthy human being. It was therefore not surprising to find a broad range of values for the elements of the bone marrow in normal rats. Because of this, attempts to express the results in averages, or as means, with standard deviations, seemed to have little value. Tables were constructed to show the range, the mode, and the number of rats falling in the mode and below and above it.

Discussion. The study of hemopoiesis in pre- and post-natal life has given rise to several theories regarding the origin of blood cells. The polyphyletic, or tri-

istie, theory briefly states that the reticulo-endothelial cell gives rise to an extra-vascular, or "free cell" which is present in all leucopoietic tissue: this in turn gives rise to the myeloblast, lymphoblast and monoblast. The endothelial cell lining the vascular system of the bone marrow gives rise to megaloblasts which are the progenitors of the cells of the erythroid series.

The megaloblast has been described as a large cell, with an opaque, densely-staining cytoplasm and a coarse arrangement of the nuclear chromatin. Megaloblasts may be observed in adult human bone marrow under pathological conditions. Their presence in the bone marrow of normal adult albino rats has not been reported, nor were cells of this type noted in the smears of bone marrow studied in the present investigation. In the human the myeloblast, lymphoblast and monoblast have been described as peroxidase-negative cells, with similar cytoplasmic and nuclear morphology and staining reactions, properties which render differentiation uncertain and difficult. These cells have been grouped together here under the heading of "blast" cells. It is believed that myeloblasts are preponderant, because (1) of the relatively small total number of lymphocytes and monocytes present in the marrow and (2) microscopic examination of histological sections of the femur of the rat showed only a very occasional lymphoid follicle.

The promyelocyte differs morphologically but slightly from the "blast" cell. That it is a precursor of the granulocyte is evident because of the presence of a few scattered granules in the cytoplasm. In this stage of development it is impossible to designate the cell as the precursor of a specific type of granulocyte. Töppner⁷ classifies the "ring" cell as a promyelocyte: this point is discussed below.

The myelocyte and metamyelocyte as here classified do not differ from those described by other authors.

The "ring" cell is believed to occupy an intermediate position between the myelo-

cyte and the metamyelocyte for the following reasons: (1) The opening, or "ring," in the nucleus is thought to represent a primary step in the formation of the typical indented nucleus of the metamyelocyte, (2) the staining reaction of the cytoplasm within the "ring" is frequently acidophilic, resembling that of the more mature cell, and (3) the presence of numerous granules favors an advanced position in the line of descent. It is noted, however, that no eosinophilic granules were observed in "ring" cells.

The staff cell might be classified in two separate groups on the basis of nuclear morphology. It is believed that the more immature form has the horseshoe-shaped, or elongated nucleus described by so many authors and that those cells in which the nucleus is non-lobulated and ring-shaped represent the stage in development closest to the mature cell.

The mature granulocyte described herein does not vary from that described by other authors. The presence of the basophilic granulocyte in this group is worthy of attention. No cells resembling progenitors of this type were observed. The basophile is infrequently noted in the bone marrow of the rat (Higgins and Machella²), other laboratory animals and the human (Plum⁴) (Table 1). In approximately 700 differential counts (100 cells) of the peripheral blood of rats, made in this laboratory in connection with this and other experimental procedures, only *one* basophile was observed.

The cells of the erythroid series have been divided into two groups for purposes of simplification. The term erythroblast is used to include the cells designated by others under the various headings of proerythroblasts, erythroblasts, macroblasts, pronormoblasts, etc. It is felt that to subdivide these cells on the basis of differences in size and cytoplasmic staining reaction, which does not appear to have a direct relation to size, is unnecessary and confusing. Contrasted with the normoblast the erythroblast is larger and its nucleus exhibits a definite pattern of the

chromatin. The cytoplasm of cells of both types may take similar stains, although hemoglobin tends to be present in greater amounts in the more mature elements. A high percentage of erythroblasts exhibit a dark grayish-lavender or deeply basophilic cytoplasm: these are believed to represent the more embryonic forms. It is of interest that the mature erythrocyte, both in the bone marrow and the peripheral blood of the rat exhibits a marked degree of polychromatophilia.

The lymphocyte, monocyte and plasma cell are identified here in a manner similar to that used by other workers. The polymorphonuclear leucocyte-lymphocyte ratio in the peripheral blood of rats is the reverse of that in human beings (Table 2). The percentage of lymphocytes present in the bone marrow of rats is, however, somewhat lower than that reported for man. The percentage of monocytes in the peripheral blood of rats, as in the human being is relatively much greater than that in the bone marrow. The percentage of plasma cells in the bone marrow of the rat and in that of the human being are similar.

The megakaryocytes of the rat and of the human do not differ.

According to Toppner⁷ the "kugelhäufen" has been described by Landa and Flaun and Kleiberger. They have been classified as reticulo-endothelial in origin. The "bullets", or particles of intensely dark-staining material, are of unknown origin. These cells resemble those described by Maximow and Bloom³ as macrophages (histiocytes, plasmatocytes, wandering cells) and the particles are thought to be ingested blood pigments. Smaller but similar cells are the wandering cells of the tissues, such as the "dust cells" in the lung, encountered in the human, and the "mast" cells, seen in areas of inflammatory reaction in the rat.

One of the greatest disadvantages encountered in obtaining a sample of bone marrow was the necessity for sacrificing the animal. The possibility of carrying out successive studies was thereby elim-

inated. The femoral medulla has a diameter of 1.5 to 3 mm. The bony cortex, although less than 1 mm. in thickness, is extremely hard and attempts to enter the exposed shaft in the living animal, with the needles available, were unsuccessful.

The method used eliminated contamination of the marrow by peripheral blood. The bone marrow of the rat is extremely hyperplastic: It presents a pink to reddish-gray appearance and is moderately thick in consistency. Attempts were made to count cells in undiluted marrow in accordance with the methods of Töppner⁷ and Stasney and Higgins.⁶ These counts were not accurate because of the thickness of the smears and the resulting overlapping of a high percentage of the cells. The difficulty of making a correct differentiation of cell types under such conditions is obvious. It is further believed that the counting of consecutive cells, rather than the counting of cells in selected fields, yields a more accurate estimation of the percentage of cell types present.

Counts of the various types of cells were also made on sections of femur, fixed in Zenker's solution and stained with Wohlbach's modification of the Giemsa stain. The shrinkage of cells during fixation rendered identification difficult.

The differential counts made on peripheral blood of the 12 rats fell within the normal limits of many counts not only as made in this laboratory but also as reported by others (Griffith and Farris¹; Scarborough⁵).

Summary. A new technique for obtaining smears of femoral bone marrow of the rat is detailed.

The types of cells observed in the femoral bone marrow are described and their interrelationships discussed.

On the basis of morphologic studies of the femoral bone marrow in 12 adult albino rats tables have been constructed to show the distribution by percentage of the various cellular elements; the range and modal values for each have been determined.

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POSTPARTUM BLOOD: ITS CLOTTING MECHANISM AND RELATIONSHIP TO THE PERIPHERAL BLOOD PICTURE

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THAT menstrual blood is a unique non-clotting fraction has been long known, and its "coagulation defect" has been repeatedly studied.^{2,6,8,9} The non-clotting nature of postpartum blood has also been observed,⁷ but we know of no studies as to the etiology of this phenomenon. Because of the potential value of such information in the management of the pregnant patient with hemorrhagic disease and in the problem of postpartum hemorrhage, the clotting mechanism of postpartum blood, its nature and its relationship to the clotting mechanism of the circulating blood have been studied.

Postpartum blood was collected by 2 methods: (a) 1 hour after delivery a vaginal diaphragm was put in place which was removed from 2 to 12 hours later and the contained specimen studied, or (b) a sterile 50 cc. test tube was held in the vagina above the level of the episiotomy wound and the fundus gently massaged as the specimen was collected directly. All peripheral blood samples used for comparative studies (defibrinated, heparinized, clotted, etc.) were human blood. Since it was immediately determined that postpartum vaginal blood has both the blood type and Rh classification of the circulating blood, in all procedures which involved mixing peripheral and postpartum blood (clot lysis, seeding, etc.) both samples were taken from the same patient. The thromboplastin employed was the standard material used for prothrombin determinations (Difco). The crude human fibrinogen (Lilly) and the thrombin (Parke-Davis) were issued for investigational use. Clotting times were determined at room temperature by the method of Lee and White.¹²

Procedures and Results. No. 1. Postpartum blood does not clot spontaneously and will not clot when any of the following

elements are added singly: calcium, trypsin, fibrinogen, thromboplastin, thrombin. The single absence of any of these substances, or the presence of a specific inactivator against one of these is therefore ruled out. This also eliminates an analogy with oxalated and citrated blood, which clot on the addition of calcium; as well as with heparinized blood and recalcified plasma, both of which clot on the addition of thrombin. For control purposes in the further studies, accordingly, these incoagulable forms were not used. Control experiments were run with defibrinated blood, prepared by the glass bead method and "serum plus cells." This latter fraction was made by resuspending the patient's saline-washed cells in her own serum in a concentration adjusted to approximately 50% of the original red cell count.

No. 2. 0.1 cc. of postpartum blood and of the control bloods were placed in test tubes and 2 cc. of freshly drawn venous blood was added to each. The clotting times so obtained were repeatedly consistent, the results in a single typical experiment being shown in Table 1. It can

TABLE 1.—CLOTTING TIMES OF VENOUS BLOOD (2 CC.) WITH ADDITION OF BLOOD FRACTIONS UNDER EXAMINATION (1 CC.)

Substance added	Minutes
Nothing (Control)	6
Oxalated plasma	6½
Defibrinated blood	3
Cells plus serum	2½
Postpartum blood	3

be seen that there is no evidence of an anticoagulant in any of these bloods, but rather a clot-promoting activity. Such clot-promoting action on normal blood is not possessed by citrated blood.⁹

No. 3. While the failure to clot on the addition of thrombin would point to a

deficiency in fibrinogen, the single addition of fibrinogen, as indicated above, failed to produce clotting. Two mixtures were prepared, therefore, 1 of thromboplastin and thrombin, the other of thromboplastin and fibrinogen. One cc. of each mixture (*i. e.*, an excess) was added separately to 1 cc. samples of the bloods under study. The results of a typical experiment are shown in Table 2. In its reaction to

TABLE 2.—CLOT FORMATION ON ADDITION OF THROMBOPLASTIN AND THROMBIN (No. 1) AND OF THROMBOPLASTIN AND FIBRINOGEN (No. 2) IN EXCESS

Blood studied	Mixture No. 1	Mixture No. 2
Defibrinated	No clot	Clot
Serum plus cells	No clot	Clot
Postpartum blood	No clot	Clot

thromboplastin, fibrinogen and thrombin, therefore, postpartum blood behaves like defibrinated blood or a suspension of cells in serum.

No. 4. When postpartum blood is "seeded" with small amounts of fresh unclotted venous blood, clotting occurs.⁷ By repeated determinations with serial amounts of venous blood added, it was found that the minimal amount which would produce this phenomenon was about 2 drops per cc. of vaginal blood. It was also determined that the addition of this same amount of oxalated blood, serum or plasma was ineffective in producing clotting. Defibrinated blood and serum plus cells show the same "seeding" reaction and will clot when 2 drops per cc. of freshly drawn venous blood are added. This phenomenon may well account for the postpartum clots occasionally passed (*i. e.*, the seeding from small cervical tears).

No. 5. The proteolytic action of menstrual blood has been reported.⁸ A possible proteolytic activity in postpartum blood was investigated as follows: samples of 1 cc. of postpartum blood were incubated at 37° for 48 hours against each of the following: 2 cc. clotted blood (drained of its serum), crude human fibrin, washed from the beads following the defibrination of 30 cc. of blood, and 2 cc. of

serum clotted by the addition of minute amounts of fibrinogen. In each case the substrate was weighed before and after incubation, and the digestion expressed as % of weight lost. Since these figures are determined from wet weights, they are subject to error and must be interpreted liberally. The average of 5 determinations in each case was taken, and are shown in Table 3. It can be seen that postpartum

TABLE 3.—THE PERCENTAGE OF WEIGHT LOSS OF CLOT FRACTIONS WHEN INCUBATED 48 HOURS WITH POSTPARTUM BLOOD

Substrate	Weight loss	
	Control (%)	Digested (%)
Fibrin	8	16
Clotted serum	10	45
Whole clot	15	50

blood displays no tendency to lyse crude fibrin, and that its lytic action against clotted serum and whole blood clot, while definite, is not marked. A more pronounced lytic action has been reported for other body fluids and extracts.⁸

COMMENT. The data developed from the above experiments indicate that the blood discharged from the uterus in the postpartum period behaves in its clotting reactions like defibrinated blood. It has a weak proteolytic action, and a clot-promoting activity. Since its behavior is essentially that of a suspension of cells in serum, 2 questions immediately arise: (a) Is the cell content constant, or does it fluctuate, and what is its relation to the cellular elements in the circulating blood? (b) Is its chemistry that of the patient's serum?

No. 6. Complete cell counts and differential determinations on the peripheral and uterine bloods were made daily on 10 patients for a period of 5 days postpartum. The results are indicated in Figure 1. It can be seen that the red cell content and hemoglobin never equal those of the circulating blood, and diminish daily. Due to persistent clumping, which was overcome with difficulty, the white cell count is less accurate, but it starts at a low level and rises rapidly, exceeding

the peripheral count in all cases within 36 hours of delivery. Although the lymphocyte count of the vaginal blood tended consistently to be lower, the difference was not great, and the differential count of the vaginal blood in general roughly reflected that of the peripheral

blood. The platelet count was in all cases low (average 36,000 per c.mm.).

No. 7. Routine chemical studies were carried out on specimens of vaginal blood collected the 1st day, controlled by similar determinations on the patient's circulating blood. Blood chloride and cholesterol

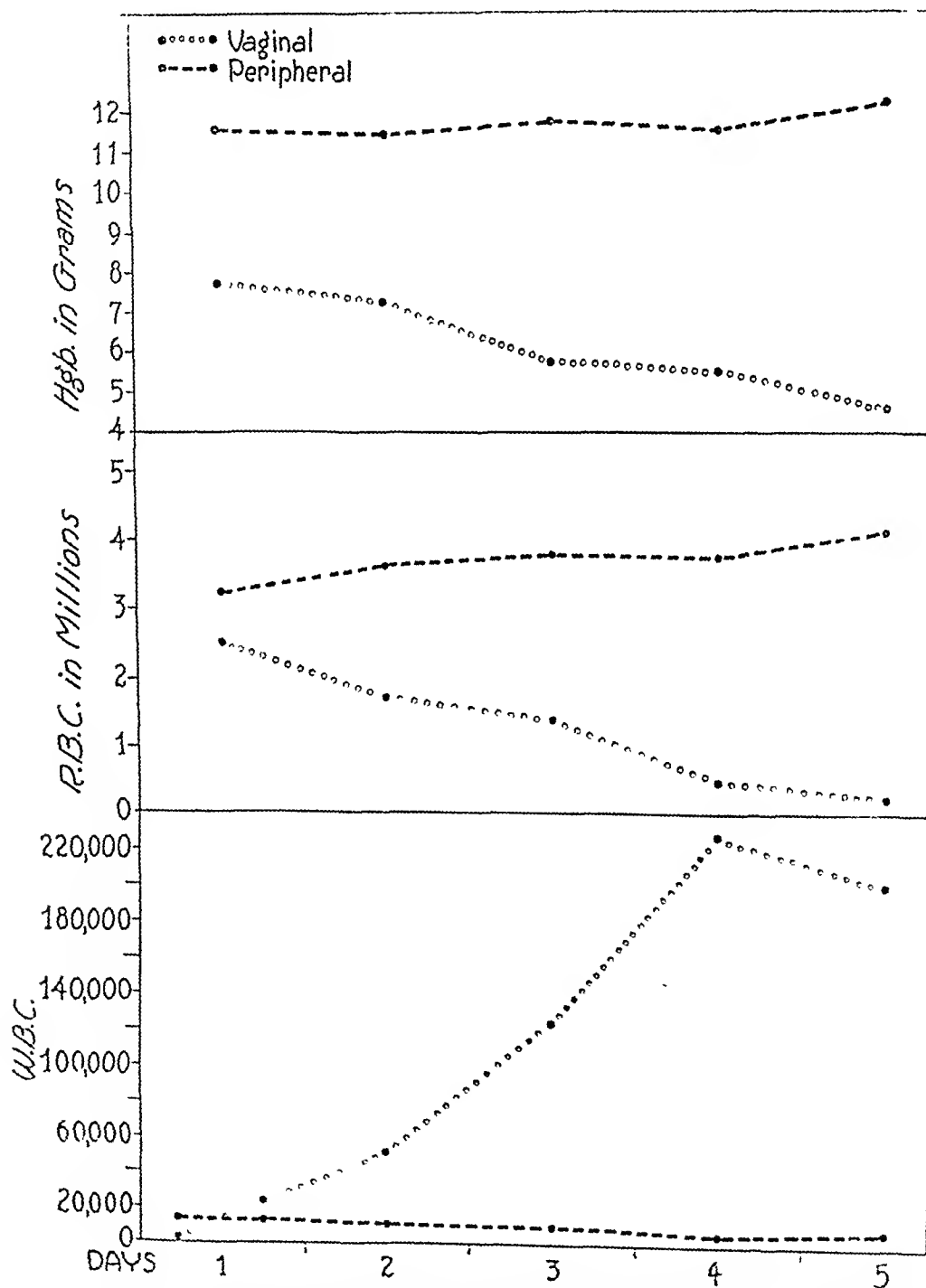


FIG. 1.—Composite chart of the changes in hemoglobin, red cell, white cell elements of the postpartum blood during the first 5 days of the puerperium.

levels were normal, as was the sedimentation rate. We did not discover in postpartum blood the elevated nitrogen levels reported for menstrual blood,¹¹ and the NPN and BUN on 7 samples of blood consistently ranged on the low side of normal, with the exception of a single BUN determination of 32 mg. It should be noted that all of the above results (whole blood determinations) were within normal range, but that in all (except the single BUN cited), the levels discovered in the vaginal blood were lower than those in the venous blood. These results conform with the hypothesis that vaginal blood is serum containing cells and cellular debris but with a lower count than the peripheral blood.

Serum calcium levels closely approximated those of the circulating blood, and the sugar levels were normal on specimens collected by test tube and examined promptly. The total proteins of the vaginal blood were reduced slightly (average 5.7), the loss being in the albumin fraction (average 3), with the A/G ratio approaching 1. This, however, agreed roughly with the control (venous) blood determinations which similarly showed a lowered albumin level (average 3.15).

COMMENT. Postpartum "blood" appears to be a serum-plus-cells suspension in which the cellular elements vary daily, but with a fairly constant pattern in their variation. It has no coagulation time, and since it will not clot on the addition of calcium and thromboplastin, no prothrombin time. Teleologically speaking, it is not meant to clot. The process of clot formation within the uterine cavity has nothing to do with the blood coming from the postpartum uterus. A question immediately arises which is of interest and importance both in the problem of postpartum hemorrhage as well as in the management of the puerperium in patients with blood dyscrasias: What is the relationship between the amount of postpartum blood lost and the clotting mechanism of the peripheral blood?

No. 8. By means of dicoumarol and

heparin administered in the early puerperium, the prothrombin time and the coagulation time were prolonged while the amount of vaginal blood lost was measured. The method of measuring vaginal blood loss and the experimental details have been described in the portion of this work reported.¹ The results of 10 control patients contrasted with 20 patients receiving dicoumarol are shown in Figure 2. It can be seen that the blood loss for the group with depressed prothrombin levels (Quick method) did not differ essentially from the blood loss of the control group.

Figure 3 indicates the results obtained when the clotting time was prolonged with heparin in 6 patients during the 1st postpartum day. Again it can be seen that there was no increase in the amount of uterine bleeding. Similarly, a group of patients were given vitamin K during labor to determine if there was any diminution in blood loss. One ampule of hykinone administered during labor, however, failed to raise the already elevated prothrombin level, and the blood loss suffered by this group (6 patients) was exactly that of the control group.

Discussion. It can be concluded from the above that there is a complete divorce between the prothrombin and coagulation times of the circulating blood, and the amount of blood lost from the uterus in the puerperium. While such conclusions have considerable importance in the management of the patient with hemorrhagic tendencies, it must be stressed that they apply only to blood coming from the uterus. A cervical laceration or an episiotomy in such a patient could be expected to bleed as freely as would a laceration or an incision elsewhere on the body. Furthermore, these experiments warrant conclusions only with reference to uterine bleeding after the placenta has been delivered. Blood coming from the uterus during pregnancy or labor is a normally clotting fraction similar in behavior to venous blood.

Changes in the clotting and prothrombin mechanism alone do not reproduce the

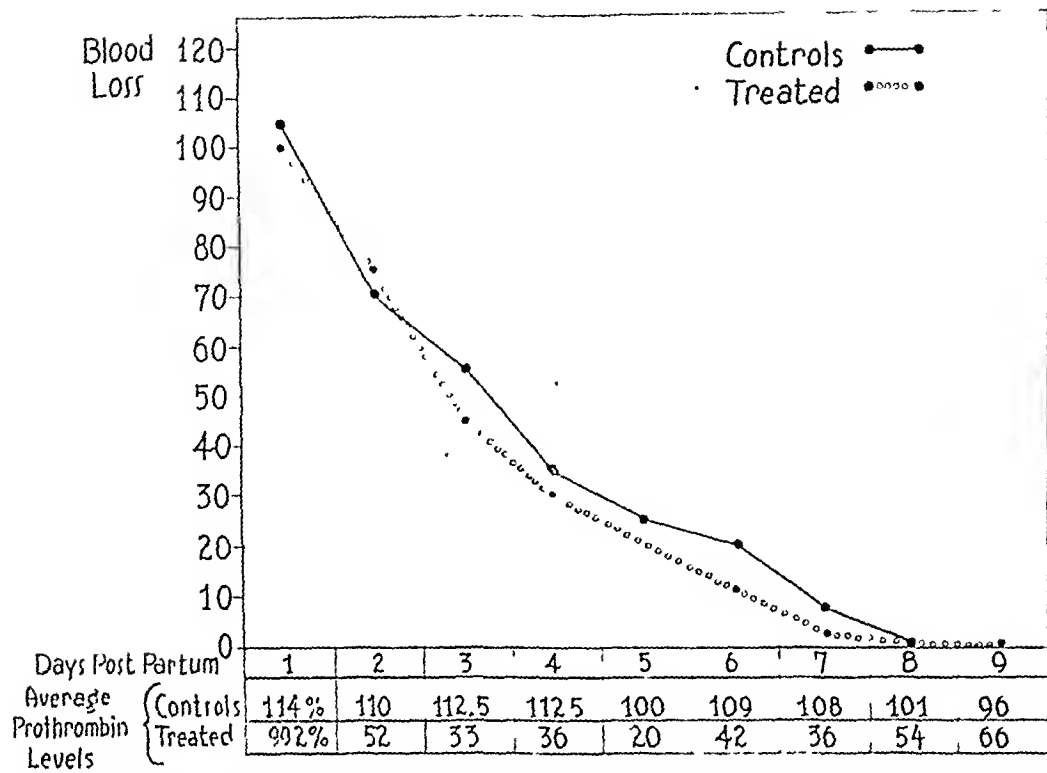


FIG. 2.—Blood loss measurements reported in terms of an arbitrary scale for a group of control patients in the first 9 postpartum days contrasted with a group of patients who received dicoumarol to depress the prothrombin levels.

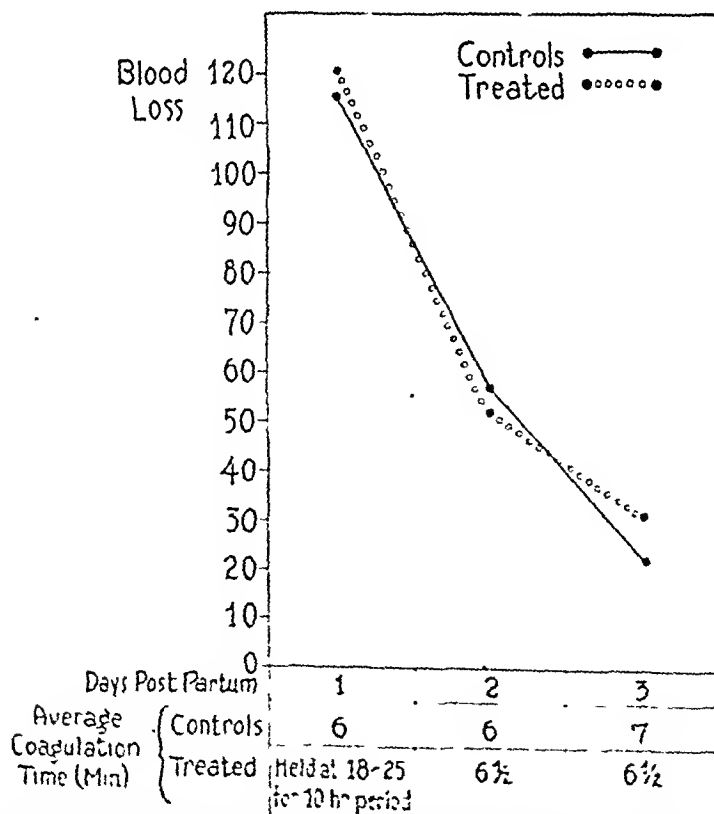


FIG. 3.—Blood loss during first 3 postpartum days of a group of control patients contrasted with a group receiving sufficient heparin the 1st day to elevate the clotting time for a 10 hour period.

picture in the thrombocytopenias. The platelet count cannot be so conveniently and temporarily altered on an experimental basis, but during the course of this study an opportunity presented itself to deliver a patient with monocytic leukemia. Her platelet count at the time of delivery was 68,000 and she had been displaying generalized hemorrhagic tendencies during the 6 days prior to the onset of labor. Immediately following delivery she was put on the same oxytocic schedule as the group of control patients cited in Figures 2 and 3 (ergotrate, $\frac{1}{32}$ gr., intravenously, following the delivery of the placenta, and by mouth 3 times a day the 1st and 2nd postpartum days). Her blood loss during the first 24 hours postpartum was about two-thirds that of the controls, and by the 2nd day had fallen to a level which could not be measured with accuracy. Bright and Hayes³ have noted in a recent report of a patient with acute lymphatic leukemia in pregnancy that "postpartum hemorrhage, contrary to expectation, was easily controlled." Such an "expectation" is based on the assumption that the clotting defect in the circulating blood will be reflected in the amount of postpartum bleeding. It is interesting to note, however, that in the 76 cases of leukemia in pregnancy collected by McGoldrick and Lapp¹⁰ there is only 1 death from postpartum hemorrhage recorded (attributed to uterine atony). Another postpartum death occurred from bleeding, but the patient had been subjected to Cesarean section and the possibility of the bleeding being from the uterine and/or abdominal incisions is not ruled out. Finn⁴ in his survey of the literature and report of cases of thrombocytopenic purpura in pregnancy states that "most authors agree that no hemorrhage occurs at the time of delivery." From our own experience, therefore, as well as from the reports in the literature, the influence of a diminished platelet count on postpartum bleeding is apparently not the same as is its reported effect on menstruation.⁵

Abnormal bleeding states are usually

associated with one or more of the following: (1) alterations in the clotting mechanism; (2) qualitative or quantitative changes in the platelets; and (3) increased permeability in the capillary wall.¹³ On the basis of experimental alterations in coagulation and prothrombin times reported here, and of observed and reported cases with lowered platelet counts, it is apparently possible to draw the conclusion that there is little, if any, relationship between the first and second groups of changes and the tendency to bleed excessively during the postpartum period. The ability of the blood to clot, the normal body defense against blood loss, apparently plays little part in the problem of postpartum uterine hemorrhage. The relationship of capillary permeability remains to be investigated, but undoubtedly the most important single factor influencing the amount of blood lost following delivery is the mechanical closing of the sinuses in the placental bed, which is dependent on the efficiency of the uterine contraction and unrelated to the coagulation tendencies in the circulating blood.

Conclusions. 1. The "coagulation defect" of postpartum uterine blood has been studied: (a) This blood fraction does not clot *in vitro* spontaneously or on the addition of any one of the following substances singly: calcium, thromboplastin, trypsin, fibrinogen or thrombin. Accordingly, it does not resemble oxalated, citrated or heparinized bloods, or recalcified plasma. (b) It displays a clot-promoting action and a definite but weak proteolytic activity. (c) Postpartum blood will clot on the addition in excess of a mixture of thromboplastin and fibrinogen, or on "seeding" with small amounts of freshly drawn venous blood. In these respects it behaves in a manner similar to defibrinated blood or a suspension of cells in serum.

2. Hematologic and chemical characteristics of postpartum uterine blood have been investigated: (a) Its cell count varies daily during the puerperium. (b) This variation follows a characteristic pattern,

with the hemoglobin and red cell count dropping steadily, while the white cell elements rise rapidly. (c) The blood chemical analyses give results which would be anticipated for a suspension of cells in serum.

3. The effect of variations in the clotting mechanism of the peripheral blood on the amount of postpartum blood lost has been measured: (a) Prolongation of the prothrombin and clotting times (by dicoumarol and heparin) did not increase the amount of postpartum blood lost. (b) The administration of vitamin K was without effect in raising the (already cle-

vated) prothrombin level of the patient immediately postpartum, and was without effect in diminishing vaginal blood loss. (c) A patient with monocytic leukemia and a platelet count of 68,000 at delivery had a smaller postpartum blood loss than the control patients in this series. The literature reporting thrombocytopenic dyscrasias in pregnancy shows no correlation with hemorrhage. (d) Although it has been assumed to exist, no definite relationship can be established between the peripheral blood coagulability and the amount of postpartum bleeding.

The writer is greatly obligated to Miss Eloise White for technical assistance.

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THE EFFECT OF CIRCULATORY FACTORS ON THE BROMSULPHALEIN TEST IN LIVER DISEASE

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THE bromsulphalein test, introduced by Rosenthal⁷ in 1922 and elaborated by Rosenthal and White⁸ in 1924, has had wide clinical trial over a period of many years. It has a prominent position among tests of liver function because of its ease of performance and specificity as a test for hepatic excretory capacity. However, it is inadequate in disclosing minor grades of hepatic dysfunction in local lesions which do not encroach upon the liver's reserve of original or regenerated tissue. But, once damage is sufficiently extensive to be demonstrated by the test, its value is enhanced by serial repetition to indicate quantitative fluctuations at appropriate intervals. The recent adaptation of the photoelectric method in the determination of bromsulphalein retention should further increase its usefulness by eliminating the difficulty in matching icteric sera.

A method which involves the introduction of a dyestuff into the circulating blood stream, its excretion almost exclusively by the hepatic cells, and the measurement of the dye remaining in the blood stream after a given time, involves but 2 factors: namely, the functional status of the liver with regard to dye excretion, and the functional integrity of the blood circulatory system. For many years, the intimate connection of circulatory insufficiency and hepatic dysfunction has been studied. Frequently the bromsulphalein test has been used together with the Van den Bergh reaction and others to assess hepatic insufficiency in cardiac failure. In 1930, Jolliffe⁵ using a 2 mg. per kilo body weight dosage of the dye, concluded that impairment of liver function induced by chronic passive congestion apparently was not permanent, whereas that still in

evidence after recovery from the congestion probably indicated an independent liver involvement. In 1932, Robertson, Swalm and Konzelman,⁶ studying the comparative merits of 5 liver function tests in cardiac decompensation, concluded that the bromsulphalein test gave results of less significance than did the icterus index. However, their figures on bromsulphalein retention at 30 minutes, with the 5 mg. dose, would appear to substantiate a higher evaluation. In discussing hepatic function in portal cirrhosis and congestive heart failure, Cantarow³ stated that hepatic functional impairment, as indicated by retention of bromsulphalein, is present in practically all cases of myocardial failure with hyperbilirubinemia. Boland and Willius,² concluded that in cases of congestive heart failure, minor grades of dye retention were disclosed frequently, whereas marked degrees of impairment of hepatic function were uncommon. However, it remained for Bernstein, LeWinn and Simkins¹ to attempt more precise methods of evaluation of the purely circulatory and purely hepatocellular components in the production of demonstrable bromsulphalein retention in heart disease. In 59 cases they reported the bromsulphalein (5 mg. dose) test, venous pressure readings, magnesium sulphate and ether circulation time determinations, and clinical evaluation of the patients. They found that the dye excretion was normal in the absence of heart failure, that mild degrees of heart failure appeared to present parallel impairment of the bromsulphalein and circulation time tests, that bromsulphalein retention was nearly always present in severe grades of heart failure. However, no mathematical

correlation was demonstrable. Chávez, Sepúlveda and Ortega,⁴ utilizing several hepatic function studies in heart failure, concluded that blood bilirubin, bromsulphalein and urinary urobilinogen determinations were perceptibly parallel and usually correlated with the degree of heart failure. They did not attempt the differentiation of circulatory and hepatic factors suggested by Bernstein, *et al.*

With the foregoing observations of hepatic function in known cardiac disorders in mind, we investigated the status of the test in known cases of hepatobiliary disease in which cardiovascular disorders were coexistent to determine possible effects of impaired circulation. A group of 14 patients with hepatic disorders and clinically established cardiovascular abnormalities were followed over a period of time. The procedures used were the bromsulphalein test, venous pressure reading, and circulation time determination, performed in that order. In the bromsulphalein test the dose was 5 mg. per kilo and a single specimen was taken at exactly 30 minutes. The standard of normality was 10% or less retention. On withdrawing blood for the 30-minute specimen, an L-tube manometer was attached for direct measurement of the venous pressure in centimeters of blood. When that measurement was concluded, 2.5 cc. of 20% calcium gluconate was rapidly injected through the same 18-gauge needle, and the arm-to-tongue circulation time determined. Thus, the entire procedure could be accomplished with but 2 venipunctures. Venous pressure readings between 4 and 12 cm. were considered within normal limits and the normal range of circulation time was taken to be 9 to 16 seconds. In some instances, to reduce discomfort and anxiety to the patient, the venous pressure determination was omitted.

The diagnosis of liver disease in this group was established by standard clinical and laboratory observation, the latter including determinations of icterus index, Van den Bergh reaction, urobilinogen

studies (Wallace and Diamond technique), galactose tolerance test, cholecystography and, in some instances, biliary drainage. The group included cases of acute infectious hepatitis, chronic hepatitis following that disease, metastatic carcinoma of the liver, and hepatic cirrhosis. In each instance, particularly in the cirrhotic patients, care was taken to exclude cases in which any direct relationship could be established between the cardiovascular and hepatic factors etiologically. Although none of these patients are known to have come to autopsy at this time, we believe that throughout the group these 2 entities have been relatively separate insofar as clinical observation, hepatic function tests, electrocardiography, radiologic cardiac measurement, venous pressure, and circulation time could tell. Results of the study are detailed in Chart 1.

Discussion. While no major generalizations can be drawn from this comparatively small series of cases, there would appear to be some justification for certain limited conclusions. It is obvious that in each case, the excretion of bromsulphalein has been infringed upon by the dual factors of hepatic disease and circulatory inefficiency. Just as in the cases described by Bernstein, *et al.*,¹ it is equally clear that no mathematical formula by which a percentage role could be assigned to the individual components is indicated by this study. Nevertheless, it is of interest to examine certain aspects of the results.

In the acute infectious hepatitis group, Cases 2 and 4 underwent some break in compensation for which we can offer no adequate explanation. In each instance, presumably, the patient was on bed rest and, as far as could be ascertained, there was no relapse of hepatitis demonstrable by fever, re-enlargement of the liver, palpation or rebound tenderness or alteration in icteric index. Unfortunately, neither methylene blue nor readily performed quantitative urinary urobilinogen techniques were available at the time. However, over and above the abnormal brom-

sulphalein readings made from 4 to 8 days prior to the break in compensation, there occurred a notably increased bromsulphalein retention associated with abnormality of the circulation time and venous pres-

sure. Once compensation was restored and circulation time and venous pressure had returned to their normal or former levels bromsulphalein readings were found to have decreased even below their prior

CHART 1

ACUTE INFECTIOUS HEPATITIS

Case	Age	Interval Between Tests	Clinical Data	Bromsulphalein	Circ Time	Ven Pres	Hep Enl (Cm)
1	29	14 d	Convalescent, old mitral stenosis, compensated	20	18		0
		29 d	Mild relapse of hepatitis with break in compensation, basal rates	70	20		2
2	26	29 d	Convalescent; compensation restored	20	19		0
		8 d	Convalescent; old mitral stenosis, compensated	20	16		1
		22 d	Icterus index unchanged at 10 units but mild pulmonary congestion	45	23	16	3
3	41	22 d	Compensation restored, no hepatic activity	10	17	10	0
		14 d	Peak of mild hepatitis, old mitral stenosis, compensated	60	17	10	3
		21 d	No change in cardiovascular status	20	19	10	0
		21 d	Convalescence complete	10	19	10	0
4	34	1 d	Convalescent, aortic stenosis, compensated	20	18	12	1
		1 d	Frequent ventricular extra-systoles and mild dyspnoea at rest	35	22	17	2
		30 d	Normal rhythm and compensation, icterus index unchanged	18	18	12	0
5	26	11 d	Convalescent; mitral stenosis, compensated, icterus index 8 units or less 15 days	10	11	9	0
		10 d	4th day of exercise tolerance series icterus index 9 units, moderate dyspnoea on walking	35	18	13	1
		10 d	Complete rest during interim, no evidence of broken compensation after 3rd day, icterus index 9	10	12	8	0

CHRONIC HEPATITIS

6	27	.	Mitral stenosis compensated, apparently normal convalescence from acute infectious hepatitis Icterus index 17 units 6 weeks after inception of jaundice	60	14		2
		1 mo	Good compensation, icterus index 11	25	15	9	1
		2 mo	Icterus index 14 units, continued fatigability, hepatic rebound tenderness	25	15	8	2
		2 mo	3rd day of exercise tolerance test with icterus index 17, serum proteins 6.0 gm, A/G ratio 2.4, mild dyspnoea at rest	55	20	12	4
		1 mo	Complete bed rest since last observation, icterus index 14, rebound hepatic tenderness, anorexia	25	14	8	2

METASTATIC CARCINOMA OF LIVER

7	64	.	Primary lesion stomach Generalized arteriosclerosis with radiological evidence all extremities Icterus index 9, serum proteins 6.3 gm, A/G ratio 2.1	10	13		1
		2 mo	During 36-hour attack of mild dyspnoea bilateral basal rales mild dependent edema, serum protein 6.2 gm, icterus index 10, A/G ratio 2.3	25	19	16	3
S	49	3 w	Complete bed rest during interim icterus index 10 units	14	12	9	1
		3 w	Primary lesion right breast Primary pernicious anemia without anemia generalized arteriosclerosis B P 180/110 Icterus index 12, serum proteins 5.9, A/G ratio 2.2	25	13	12	2
		3 w	Brief phase of moderate dependent edema and moderate dyspnoea with few basal rales, B P 170/120 Icterus index 10, serum proteins 6.1 gm, A/G ratio 2.0	45	20	16	1
		1 mo	No evidence of broken compensation, B P 170/100 Icterus index 10 serum proteins 6.1 gm, A/G ratio 2.2	25	14		2

PORTAL CIRRHOSIS

9	52	.	Chronic glomerulonephritis with hypertension mild icterus no edema or ascites, ambulatory	45	15		1
		2 mo	No ascites, mild dependent edema serum proteins 6.7 gm, A/G ratio 1.9	70	21		1
		15 d	Complete rest, no medication, no edema	35	16		1
10	49	.	Hypertensive cardiovascular-renal disease, compensation apparently intact, early cirrhosis, secondary to hepatitis 4 years previously	30	15		2
		3 mo	48 hours after auricular fibrillation of 24 hours' duration	60	19		2
		4 d	Digitalized	40	16		2
		1 mo	No medication, no evidence of circulatory embarrassment	40	15		2
11.	36	.	Mitral stenosis, compensated, intermittent icterus; no ascites	35	18	12	1
		5 mo	Compensation intact, continued intermittent icterus, no demonstrable ascites but superficial venous anastomoses more prominent	40	18	12	1
12	42	.	Essential hypertension, B P 210/115, early cirrhosis with slight intermittent icterus up to index of 20 units	30	14	11	2
		3 mo	Icterus constant, B P 205/115 Icterus index 18, serum proteins 5.2 gm, A/G ratio 1.2	45	14		0
		7 mo	Icterus index constant 22 to 24 units, B P 220/120 Serum proteins 4.8 gm, A/G ratio 0.8, possible slight ascites	55	18	16	0
13	56	.	Generalized arteriosclerosis early cirrhosis B P 155/95 Slight jaundice no ascites History of alcoholism	30	14	10	2
		5 mo	Intermittent jaundice with icterus index up to 24 units, serum proteins 5.2 mg, A/G ratio 1.4	35	11		2
		6 mo	Jaundice deeper, hemorrhage from esophageal varices B P 170/110 Serum proteins 5.0, A/G ratio 1.0 Icterus index 23 to 28 units	55	22	16	0
14	62	.	Generalized arteriosclerosis moderately advanced cirrhosis with peripheral anastomotic circulation B P 160/95 constant mild icterus, no ascites	45	15	9	1
		3 mo	Clinical condition essentially unchanged	45	14	10	(?)

("Hep Enl.") refers to palpable hepatic enlargement below costal margin in mid-clavicular line.

figures. It would appear in these 2 instances that hepatic regeneration and repair had proceeded normally regardless of the intercurrent circulatory insufficiency. In Case 6, on the other hand, in which significant decreases of dye excretion were precipitated by exercise tolerance studies, it is possible that the ineffectiveness of exercise effected the change through the medium of either factor; that is to say, through either the induction of an hepatic relapse or an untoward circulatory strain, or, possibly, both. All findings in the case were at a relative standstill approximately 6 months after the onset of the acute phase of hepatitis, and it was felt that the patient was entering upon a chronic status at the time when exercise tolerance studies were begun; by the third day, there was perceptible increase of scleral icterus, the patient was mildly dyspneic on complete rest, temperature was normal, appetite decreased sharply, and general malaise and moderate non-productive cough supervened. It was at that point that the bromsulphalein retention sharply rose from 25% to 55%, the hepatic size and tenderness increased, the circulation time shifted from 15 seconds to 20, and the venous pressure rose to a high normal level. It is quite possible that both circulatory and purely hepatic degenerative components played independent or interdependent roles in this episode. The return of all values to former levels after 1 month of bed rest might equally well have occurred as a result of improvement in either factor.

The 2 instances of metastatic carcinoma of the liver here cited appear to reflect almost wholly the influence of circulatory decompensation on the bromsulphalein test. In each instance of this comparatively slowly progressive process, the significant alteration of dye retention coincident upon break in compensation was attended with parallel circulatory dysfunction as revealed by the circulation time and venous pressure data, and all returned to their former corresponding levels with apparent restoration of com-

pensation. At the same time, there was no evidence, clinically or in alteration of blood proteins, icterus index or other findings to indicate acceleration of hepatic damage or intercurrent hepatitis.

Cases 9 and 10 of the cirrhosis group were quite similar in displaying marked alteration of the bromsulphalein retention during phases of cardiovascular incompetence in which the clinical status of the cirrhotic process remained relatively unchanged. They too, reverted to their former levels of bromsulphalein retention, circulation time and venous pressure upon subsidence of the decompensation. On the other hand, Cases 12 and 13, in which no loss of compensation was known to have occurred over periods of 10 and 11 months, respectively, presented progressive failure of dye excretion which was attended with abnormal circulation time and venous pressure readings only when the cirrhotic process itself was far advanced and complicating factors such as ascites (Case 12) and hemorrhage from ruptured esophageal varices (Case 13) had entered the picture. Cases 11 and 14 were not followed over a sufficient period to have entered that phase, nor did either present any evidence of circulatory breakdown during the period of observation.

In general, therefore, it may be said that the series here described gives concrete evidence of both factors concerned in the mechanism of bromsulphalein retention,—hepatic excretory dysfunction and circulatory inadequacy. As previously mentioned, there does not appear to be any present method for delineating the proportion of influence to be assigned to each factor where both are operative in the same patient. However, the data suggest the advisability of performing studies of circulatory integrity in those cases of liver disease in which there is clinical evidence of concomitant cardiovascular involvement. While it is evident that those instances in which such circulatory studies are abnormal will fail to indicate the proportion of abnormal dye retention due to either factor, it is equally true that

those in which circulation time and venous pressure are normal will present confirmation that the abnormal bromsulphalein retention can then be attributed solely to hepatic dysfunction. It is, therefore, suggested that in the performance of the bromsulphalein test in cases of hepatic disease occurring in the presence of co-existent cardiovascular abnormalities, the circulation time, with or without venous

pressure readings, be determined, with a view either to ascertain possible circulatory factors in the retention of the dye or to establish the essentially hepatic nature of the dysfunction; such a study may further provide a basis for the evaluation of subsequent changes in either aspect of the patient's progress as determined by repetition of the tests at appropriate intervals.

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MENOPAUSAL HYPERTENSION: A CRITICAL STUDY

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THE female menopause, whether natural or artificial, has long been regarded as a cause of arterial hypertension and the concept of "menopausal hypertension" has gained wide acceptance. Yet the evidence on which this view is based is largely derived from accumulated impressions rather than systematic study. With this in mind, we undertook the care of 200 menopausal women, 179 of whom had been surgically castrated and all of whom desired relief of menopausal symptoms.

Examination of the patients was conducted in such a way that a careful record was kept of both physical and mental abnormalities. Hypertension was considered present if any reading exceeded 149 mm. Hg systolic and 94 mm. diastolic. Some of the patients were treated with estrogens, thyroid substance, or the two combined. Others received sedatives, placebos and reassurance.

If lack of ovarian secretion were truly a cause of increased arterial pressure many of these patients would manifest arterial hypertension. Since most of them were young, the problem of analysis was not complicated by their having reached the age when hypertension would in any event be present in at least a quarter of the group.¹

Results. The results of this time-consuming investigation can be summed up very briefly (Table 1). One hundred seventy-nine of the 200 women were castrated and the remaining 21 had clear evidence of ovarian failure. The ages ranged from 20 to 59 years. Thirteen per cent exhibited arterial hypertension, but 10% had shown this before the meno-

pause. The hypertension was not more severe after the menopause than before in any of our patients, despite the emotional disturbance associated with the syndrome.

Thus only 6 patients of the 200 developed hypertension following the menopause and 5 of these were 40 years of age or older. These patients had long histories of psychoneurotic manifestations preceding the menopause. Eighty-three per cent of these were equally common among the younger castrates and among the older patients with natural menopause. Most of the symptoms attributed to the menopause were in fact intensifications of former neurotic trends.

The vasomotor phenomena described as characteristic of the menopause were not always easily evaluated. In some, flushing was observed on occasion but usually only the history of hot flashes was obtainable, and this often dramatized by the patient's own beliefs about the climacteric. Yet these very phenomena have probably been partially responsible for the view that the menopause plays a part in the genesis of hypertension. Vasomotor instability as expressed by flushing, chilly sensations, tachycardia and perspiration, while often associated with elevations in arterial pressure, is by no means a constant accompaniment. It is easy to convince oneself of this by observing the constancy of arterial pressure during a bout of flushing or supposed "hot flash." Further, these complaints were equally common among hypertensive and normotensive persons. Clearly so-called menopausal vasomotor instability, unless otherwise defined, need not neces-

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sarily be indicative of pathologic change in arterial blood pressure.

Discussion. Hypertension was present in 13 % of the whole menopausal group, which agrees with the 14.7 % given for normal workers in the statistics of The Heart Council of Greater Cincinnati.² Twenty per cent of our patients over 40 years of age had hypertension compared with 23.4 % of the workers examined in Cincinnati. Clearly there was no increased incidence of hypertension in our patients with either artificial or natural menopause.

benefited by estrogen administration and in many cases not helped at all. Such treatment tended rather to distract the physician from concern over the more probable cause of the symptoms. This applied to both the surgically castrated patients and those with natural menopause.

Summary. A study of 179 castrated women and 21 with the natural menopause demonstrated that arterial hypertension is no more common in them than in the general population. "Vasomotor instability" as exhibited by "hot flashes,"

TABLE 1.—INCIDENCE OF HYPERTENSION AMONG 200 WOMEN AFTER THE MENOPAUSE

Age Groups	20-29	30-39	40-49	50-59	Total
Number of Cases	23	73	83	21	200
Natural Menopause	0	3	14	4	21
Surgical Menopause	23	70	69	17	179
Similar Premenopausal Hypertension	1	3	11	5	20
Hypertension Following Menopause	0	1	2	3	6

TABLE 2 —INCIDENCE OF ARTERIAL HYPERTENSION

Among 200 Women After Menopause				Among 2860 Office Industrial and Factory Workers			
Age Group	No Examined	No with Hypertension	Per cent	Age Group	No Examined	No with Hypertension	Per cent
20-29	23	1	4.3	20-29	727	62	8.5
30-39	73	4	5.4	30-39	1033	103	10.0
40-49	83	13	15.7	40-49	728	150	20.6
50-59	21	8	38.0	50-59	372	107	28.7
Total	200	26	13.0	Total	2860	422	14.7
Above 40 years	140	21	20.2	Above 40 years	1100	257	23.1

Administration of estrogens to menopausal patients with hypertension may aid in reducing the level of blood pressure, presumably by relieving some of the emotional tension, but its effects seem largely of secondary importance. The same degrees of blood pressure reduction are often observed by understanding management of the patient, or by administration of placebos or both.

When the syndrome was preceded by the neurotic symptoms, the menopause seemed to accentuate them. Patients suffering from severe neurosis were least

perspiration, and tachycardia, are not necessarily associated with hypertension and their alleviation by estrogens need not affect arterial pressure. The menopause seemed to intensify pre-existing psychoneuroses. Despite severe neurotic behavior, hypertension did not develop within three or more years except in 6 of these subjects. From these data it is concluded that the relationship of the menopause and hypertension is incidental and loss of ovarian secretion is neither a primary nor a contributory cause of arterial hypertension.

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AMYLASE LEVELS DURING MUMPS

THE FINDINGS IN BLOOD AND SALIVA

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THAT mumps can raise the serum amylase has been known for a long time^{2,4,7} but only in the past few years have the diagnostic possibilities been explored.

Murphy, Bozalis and Bieri,⁸ in 1943, described 58 tests made on 35 patients with mumps. Elevated values were found in all but 7 tests, and 4 of these were from patients in whom preceding determinations had been abnormal. Fennel,⁵ in 1944, reported increased amylase in blood and urine of an unspecified number of cases. Zelman,¹¹ in 1944, recorded the serum amylase of 89 hospitalized soldiers. On admission the levels were high in three-fourths of the group and normal in the rest, but by discharge, 2 weeks or more later, only 9% were still elevated. Of the group, 13 exhibited symptoms referable to the pancreas.

Applebaum,¹ in 1944, reported increased serum amylase in 45 of 50 patients. Curves made from the data suggested that the level rises early in the attack, stays up for a week or more during the active phase, and then subsides gradually as the swellings disappear. The author suggested that in bilateral parotitis the blood amylase may attain a higher level and maintain it longer than in unilateral disease. Haerem,⁶ in 1945, described elevation of blood amylase in 9 adults with mumps parotitis.

Candel and Wheelock³ similarly noted that of 224 adult males with mumps more than 96% showed elevations of serum

amylase during the course of the disease. About 84% of tests showed elevated values in the 1st week of illness, and the proportion fell progressively to 27.5% by the 4th week. They found that the complications of orchitis and epididymitis did not affect the amylase levels. Parallel estimations of serum lipase failed to show hyperlipasemia as occurs in acute pancreatitis. They concluded that the elevations of serum amylase are associated with parotid involvement, for the reason that such elevations have also been demonstrated after ligation, calculous obstruction, or suppuration of the parotid ducts or glands.

In the studies here reported attention has been concentrated upon the relationship between serum amylase activity and (1) day of disease, (2) gland or glands involved, and (3) level of amylase in the saliva.

SUBJECTS. The subjects of the study were 101 adult males, members of the Coast Guard and Maritime Services. All were hospitalized between February 21 and May 8, 1945, during an epidemic, having been referred for admission as soon as the existence of mumps was recognized. Prior to the onset of this illness all had been in apparent good health; 25 were 17 years of age; 37, 18 years; 8, 19 years; 5, 20 years. The ages of those above 20 extended rather evenly to the 34 year figure. The patterns of glandular involvements and extraglandular compli-

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cations were representative of what takes place in any typical outbreak of mumps. The symptoms, constitutional reactions and local inflammatory signs varied independently in severity from mild to severe.

A group of 47 "normal" controls of the same age distribution was set up as a standard of comparison for the blood determinations. This group was made up of healthy pharmacist's mates and of patients convalescent from non-abdominal infections such as scarlet fever or pneumonitis, or undergoing treatment for non-febrile genito-urinary ailments. One to 2 controls were tested with every batch of specimens from the mumps cases.

PROCEDURE. The blood specimens were collected in a dry tube in the morning, before breakfast, to avoid chylous clouding and hemolysis. The salivary specimens were also collected before breakfast. The patient's mouth would receive a preliminary rinsing with 0.6% sodium chloride solution, and then paraffin would be chewed. The saliva, which soon began to flow, was diluted at the bedside to 1:100 dilution with a Sørensen buffer of pH 6.8, and kept chilled until tested.

The tests of blood and saliva were carried out with the standard Somogyi⁹ starch iodine procedure, modified to permit 1 technician to perform many tests quickly within a limited period of time. The main modifications were the use of multiple pipettes within a constant temperature water jacket, the reliance upon the achromic rather than the erythro-dextrin endpoint in the iodine starch reaction, and the recording of the readings in minutes directly rather than in computed "units." These deviations from the standard procedure are feasible only when the amylase activity is abnormally increased or in the high normal range. They do not lend themselves to exploration of enzymatic activity in the zones of low normal and subnormal.

In considering the results the reader must remember that they were secured with biologic reagents, and that the "time in minutes" is related to the hydrolytic

changes exerted by 2 ml. of body fluid upon 8 ml. of a standard starch solution. The shorter the time for the starch iodine reactions to fade away, the greater the potency of enzyme in the test mixture.

Results. SERUM. Normals. Fifty-nine specimens from 47 healthy controls gave results which ranged from 6 to 13 minutes and beyond. Since all but 4 (93%) of these values were 7 minutes or higher, (2, 6 minutes; 2, 6½ minutes), the dividing line between normal and accelerated amylase activity has been set at 6¾ minutes, the approximate locus of the 90% statistic.

Nine of the patients used as controls were being hospitalized for acute epididymitis or orchitis. Two of these had been through an episode of mumps some years earlier and 2 others were aware of prior local trauma. With the remaining cases, classified as "mumps, non-specific," no immediate cause was apparent. There were no accompanying signs or symptoms to indicate that the mumps virus was the etiologic agent, though that possibility must nevertheless be entertained. None had increased serum amylase.

SERUM. Mumps Patients. Amylase tests were performed on 702 separate specimens of blood collected from the 101 patients at different and successive stages of their illness. The number of tests per individual patient ranged from 1 to 12. The serum amylase was found augmented in the majority of specimens (Fig. 1). This augmentation was most prominent during the first 7 days of illness. The 2nd week saw a return to normal, in most instances, though even by 18 days a few blood levels were still elevated.

With most patients the blood amylase was already elevated by the time they reported to the hospital. Six patients, however, exhibited normal values in the 1st few days of the attack, with sudden increases becoming apparent a day or 2 later, though not until the 11th day in 1 instance.

Of the patients who received 2 or more blood tests only 6 failed to show any increase. One of these displayed bilateral

sublingual infection without recognizable involvement of any of the other salivary glands. Another, with multiple salivary gland swellings, was tested only on the 6th and 13th day of illness. A third was tested only on the 4th and 5th days. These 3 patients might have been found with an elevated blood amylase at other times during their attacks, had a greater number of tests more evenly spaced been performed. The remaining 3 negative reactors received 3, 5 and 6 tests, respectively, well distributed through their attacks.

and lay in the same range as the corresponding values for the "mixed" multi-glandular patients.

In 1 patient the mumps involved but 1 submaxillary and the right testicle. In another the swelling was restricted to the sublinguals. Neither of these non-parotitis patients, in 2 tests performed with each, displayed any elevation of serum amylase.

Thirty had scrotal swelling from involvement of 1 or both testes or epididymes. In 8 the onset took place while the salivary glands were actively swollen.

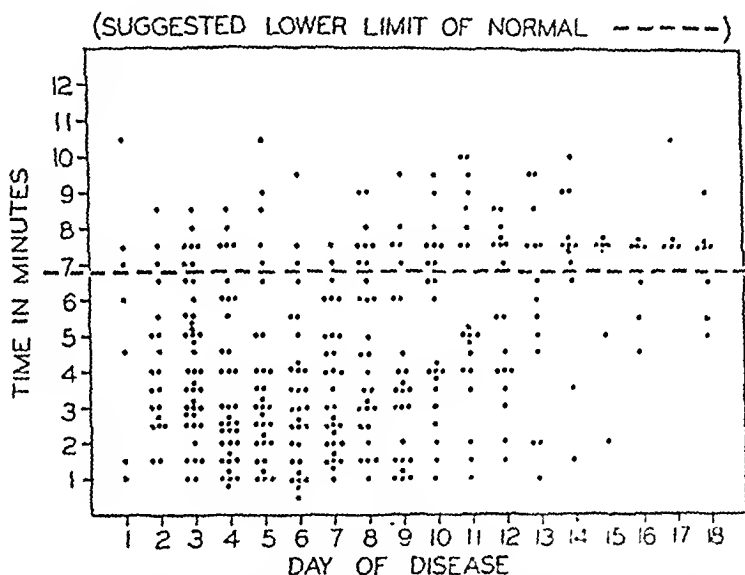


FIG. 1. -Distribution of 702 serum amylase determinations made on 101 patients in relation to day of disease. The trend of augmentation of the serum amylase level is most pronounced during the 1st week of illness, and then recedes steadily. (The shorter the time in minutes, the more potent the enzyme content of the serum.)

RELATIONSHIP TO SALIVARY GLANDS AND SCROTAL SWELLINGS. The great majority of the subjects had involvement of the parotids, 1 or both, some time during the course of the attack. One or more of the other salivary glands were usually swollen also. "Mixed" swellings were the rule.

There were 8 patients with parotid mumps in whom the involvement was unilateral, and 11 in whom the involvement was bilateral. The average and range of variation in serum amylase between the unilateral and bilateral groups were not significantly different from each other,

These 8 had elevated serum amylase, save for the 1 individual whose facial swelling was limited to the left submaxillary. In the other 22 cases, the scrotal swellings reached a peak after the glandular swellings had begun to subside. In 16 of these (73%) the serum amylase had returned to normal or was on the way down while the scrotal structures were still actively affected.

These latter observations suggest that the source of the elevated serum amylase in mumps is not the inflamed testicular or epididymal tissue. This supposition receives confirmation from the findings in

the 7 "control" cases of orchitis of traumatic or unknown origin, in whom the serum amylase level was well within normal bounds.

SALIVA. The salivary content of amylase was determined coincidentally with the serum level in 97 tests of 55 patients, and in 33 tests of 33 controls (Fig. 2).

is the infected salivary gland system. Of the 3 sets of salivary glands, the parotids are both the chief producers of salivary enzymes and the glands most commonly attacked by the virus. That the submaxillaries and sublinguals are less responsible for the blood elevation is indicated by our observation that 1 instance of pure

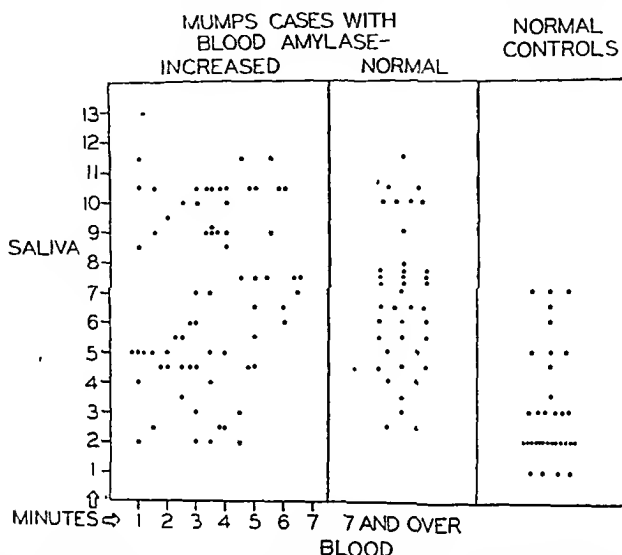


FIG. 2.—Graphic presentation of the correlations between the amylase level of serum and saliva as determined simultaneously in 97 tests with 55 patients. The values for the saliva of the control group themselves within a somewhat lower (and therefore more potent) range than do the values of the mumps patients, with or without increase of the blood serum amylase.

Each group of values exhibited a broad scatter. There were no evident correlations between serum amylase and saliva amylase. The amylase content seemed a little higher in the saliva of controls than in the mumps patients. This suggests that in mumps the content of diastatic enzyme in fasting saliva may be depressed.

Comment. These studies offer no confirmation to the hypothesis of Dunlop⁴ that the augmentation of serum amylase in mumps is produced by parenchymal pancreatic involvement. None of our patients complained of gastro-intestinal or upper abdominal symptoms, even though mumps pancreatitis often appears during epidemics.^{6,10}

It seems more reasonable, as most workers have pointed out, that the source of the increased blood amylase in mumps

submaxillary involvement and 1 instance of pure sublingual involvement failed to develop any increase in blood amylase. In Applebaum's series,¹ similarly, when the disease of the salivary glands was exclusively extraparotid, as in 2 cases of submaxillary and 1 of sublingual inflammation, the amylase was normal.

Summary and Conclusions. 1. An analysis is presented of 702 serum amylase tests carried out on 101 adult males ill with mumps.

2. An elevation of the serum amylase level was nearly always present in the 1st week of illness. This increase usually faded away by the end of the 2nd week, though in several patients it was still increased in the 3rd week. Estimation of serum amylase is therefore of value as a

confirmatory test for mumps, especially with jaw swellings of obscure nature.

3. No relationship was noted between unilateral and bilateral gland involvement and the extent of the amylase increase.

4. No correlation was detected between serum and salivary amylase in random specimens of saliva. The saliva amylase

seemed slightly lower in the mumps cases than in the controls.

5. The evidence suggests that the increase in serum amylase comes from the inflamed parotids, rather than from the submaxillary or sublingual glands, the pancreas, or the scrotal structures.

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THE FAILURE OF MASSIVE SALICYLATE THERAPY TO SUPPRESS THE INFLAMMATORY REACTION IN RHEUMATIC FEVER*

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SALICYLATES have been used in the treatment of rheumatic fever in 2 ways: as symptomatic treatment and in an attempt at specific therapy.

For symptomatic treatment in this disease the salicylates are very useful. Given in adequate doses during polyarthritides or high fever, they are very effective antipyretics and analgesics. The analgesic effect of salicylates in the arthritides of rheumatic fever is indeed so rapid that its effect is occasionally taken as a therapeutic test in the differential diagnosis of the arthritides.

The present study is concerned with the other use which has been advocated for salicylates in rheumatic fever, that of massive salicylate therapy with the object of a specific antirheumatic effect. The advocates of this mode of treatment have claimed the advantages of a shorter period of rheumatic infection and reduction in the severity of carditis. The suggestion of prolonged treatment of rheumatic fever by large doses of salicylates is not new, nor is the belief that such doses provide a specific treatment for the rheumatic process. As long ago as 1903, Lees suggested doses as high as 300 gr. of salicylate daily⁶ to obtain a "true anti-rheumatic effect."¹² In 1906 Clarke reported the treatment of rheumatic patients with 240 gr. of sodium salicylate per day, and felt that this shortened the duration of the disease and protected the heart.

Recently the proposal of massive salicylate therapy of rheumatic fever has been revived in a paper by Coburn,⁵ with the rationale that such doses of salicylates apparently suppress the inflammatory reaction of the host and thus tend to pro-

tect the heart from damage. As a result of this report massive salicylate therapy has been adopted for rheumatic fever in a number of clinics, either experimentally or as an accepted procedure.^{1,14,23,25,26}

It appears important to consider the advisability of massive salicylate therapy for the following reasons: 1. The results presented by Coburn in his paper advocating such treatment, and in the reports of 2 subsequent attempts to confirm his results, are not unequivocal. Coburn's report of the clinical results of massive salicylate therapy deals chiefly with the shortening of the period of infection in patients so treated, as judged by the erythrocyte sedimentation rate. The effects of this treatment on cardiac complications are given in the statement that "in none of 38 patients treated by this method did valvular heart disease develop, while in 20 to 63 patients receiving only symptomatic therapy there developed physical signs of heart disease." The cardiologic criteria used are not presented for valvular heart disease or for physical signs of heart disease. His patients were young adults of 18 years or more, and in this age group cardiac manifestations and residua of rheumatic disease are less common and less severe than in children. Manchester¹⁴ also treated in this way a group of patients in naval service. He found a smaller number of significant cardiac residua among patients given massive salicylate therapy than among controls, especially if the therapy was instituted before "signs of significant carditis" had appeared. Fulminating infections did not always respond favorably, and there were 2 deaths in the intensively treated

* This work was supported by a grant from the Life Insurance Medical Research Fund.

group, on the 4th and 7th days, respectively.

Taran and Jacobs²³ gave massive doses of salicylates at the onset of rheumatic carditis to 8 children and treated 41 control patients in other ways. They concluded that "while it cannot definitely be stated that massive salicylate therapy unequivocally suppresses the rheumatic process and prevents the stigmata of heart disease, it is clear that this form of treatment makes the patients symptom-free." Wégria and Smull²⁶ gave 21 patients massive salicylate therapy, with 19 control patients. They concluded that the course of acute rheumatic fever is not shortened by massive salicylate therapy, with the reservation that earlier institution of treatment might have resulted in shortening the rheumatic episode.

2. Toxic reactions to high concentrations of salicylate in the blood are quite common. Tinnitus, nausea and vomiting are among the earlier toxic manifestations of salicylates. More severe manifestations have been reported, both as a consequence of massive salicylate therapy and otherwise. They include hypoprothrombinemia and hemorrhage,^{8,17,18,24} occasional mental changes,^{13,26} temporary deafness,²⁵ and some decrease in alkali reserve.^{8,10} Moreover, 5 patients given massive salicylate therapy intravenously for acute carditis died,^{1,14,23} either as a result of toxicity of salicylates or of failure of the treatment of carditis.

3. There have been indications in the recent literature that salicylates may lower the sedimentation rate without relation to activity of the rheumatic process. Rapoport and Guest¹⁸ showed that in 10 of 15 patients with elevated erythrocyte sedimentation rates (ESR), 4 of whom had rheumatic fever, the ESR decreased following salicylate therapy. When this treatment was discontinued the ESR often began to rise toward its initial level. They also showed a decrease in the concentration of fibrinogen in the blood of these patients, and suggested that this might be due to an effect of salicylate on the liver. The latter has been suggested

elsewhere as the basis for the hypoprothrombinemia caused by the salicylates.¹⁹ Homburger¹¹ reported similar results in patients whose elevated ESR was, in fact, not caused by an infectious disease at all, but by carcinomatosis.

These indications of a non-specific effect of blood salicylates on the ESR are important for several reasons: (1) in all 3 clinical studies mentioned above the ESR was used as the criterion of the presence of an infectious process; (2) the fall of the ESR in massive salicylate therapy was offered by Coburn as evidence of specific suppression of the inflammatory process by the drug; finally, massive doses of salicylates may interfere with the reliability of the sedimentation test, which is usually the most sensitive indication of persistent rheumatic activity.

For the above reasons, and because adequate clinical testing of the effect claimed for massive salicylate therapy would require a prolonged study, it seemed particularly advisable to examine the rationale put forth as the basis of such treatment: that high concentrations of salicylates in the blood suppress the inflammatory reaction in rheumatic disease.

The hypothesis that salicylates suppress the inflammatory reaction in rheumatic fever has been tested in 1 study thus far. Murphy¹⁶ observed 12 rheumatic patients under massive salicylate therapy with special interest in phenomena indicating inflammatory activity. The size of inflamed joints was determined frequently, and the skin temperatures over these joints were compared with the rectal temperatures. The ESR was also determined. The results of these measurements did not indicate any subsidence of the inflammatory reaction under the influence of massive salicylate therapy. In addition, Murphy observed in patients receiving this treatment such phenomena as fresh rheumatic nodules and, in 1 case, fresh polyarthritis and electrocardiographic evidence of further cardiac involvement.

The studies reported here represent another approach to the question of whether salicylates suppress the inflam-

inatory reaction in rheumatic fever or merely affect the ESR. Preliminary observations were made of the effect of salicylate on elevated ESR in non-rheumatic patients; thereafter, children with signs of active rheumatic carditis and leukocytosis as well as elevated ESR were studied during massive salicylate therapy.

Methods and Materials. The patients studied were in the wards of The Children's Seashore House for Invalid Children at Atlantic City and the Philadelphia General Hospital. Salicylates were given as enteric-coated sodium salicylate tablets or as acetylsalicylic acid. When salicylates were particularly poorly tolerated, sodium bicarbonate was added in equal dosage. The daily dose was divided into 6 equal portions, given every 4 hours, day and night. It was occasionally necessary to exceed a total of 1 gr. per pound per day, in order to attain blood salicylate concentrations² of 350 gamma per cc.

The ESR was obtained, as described elsewhere,⁹ by determining the rate during the period of free fall of erythrocytes and correcting to a 45% packed red cell volume. Leukocyte counts were done at approximately the same time of day, in duplicate.

Results. Preliminary Observations: A group of non-rheumatic patients with elevated ESR was chosen for these determinations. The object of these observations was to confirm the reports mentioned above^{11,19} that doses of salicylate such as those suggested for massive salicylate therapy in rheumatic fever can lower an elevated ESR non-specifically. Six patients with pulmonary tuberculosis were studied, through the courtesy of Dr. Harold Israel of the Philadelphia General Hospital, and 4 patients with rheumatoid arthritis. The period of administration of salicylate differed among these patients, according to the severity of their toxic symptoms. Figure 1 shows the observed changes in the ESR. The data are given in crude rates of fall, mm. per hour, since the correction for packed red cell volume was not in all cases available in this experiment.

Examination of Figure 1 shows that in all but 1 of the non-rheumatic patients

during salicylate treatment the ESR fell. In 8 of the remaining 9 patients, the rate of decrease was of the order found in rheumatic subjects under such treatment.

These observations, and similar ones quoted above, demonstrated that the fall in ESR under massive salicylate therapy was not necessarily a manifestation of specific action of salicylates in rheumatic fever. They did not, however, offer evidence against antirheumatic action of salicylates in high doses, since there remained a theoretical possibility that salicylates thus administered might produce both results: a specific antirheumatic effect and a non-specific effect on the sedimentation of erythrocytes in other patients. An experiment was therefore planned which might offer some evidence as to whether the lowering of the ESR in rheumatic patients was an indication of suppression of rheumatic activity in those patients.

Since leukocytosis provides another general indication of the persistence of inflammation, it was decided to institute massive salicylate therapy in rheumatic patients who were so active as to show not only an elevated ESR but also persistent leukocytosis, and to study the results of this treatment. The number of patients suitable for this study was sharply limited by the following considerations: (1) the rheumatic process must be sufficiently active for leukocytosis to continue for a few weeks; (2) the white blood cell count of the patient must not be affected by salicylates *per se*, to the point of reaching normal limits; (3) the patient must not be severely affected by the toxic manifestations of large doses of salicylates. Patients who satisfied all these criteria were given courses of massive salicylate therapy. The specific object was to see whether any patients would show evidence of persistent rheumatic activity despite such treatment and despite the consequent lowering of the ESR. Five such patients were found. Figure 2 shows some of the features of the clinical course of these patients.

From the clinical charts in Figure 2 it

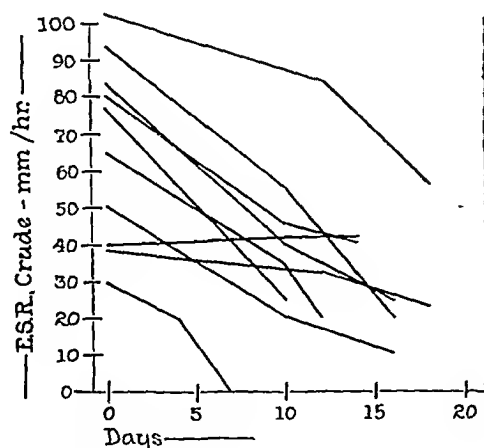


FIG. 1.—The fall in erythrocyte sedimentation rate in non-rheumatic subjects during massive administration of salicylates.

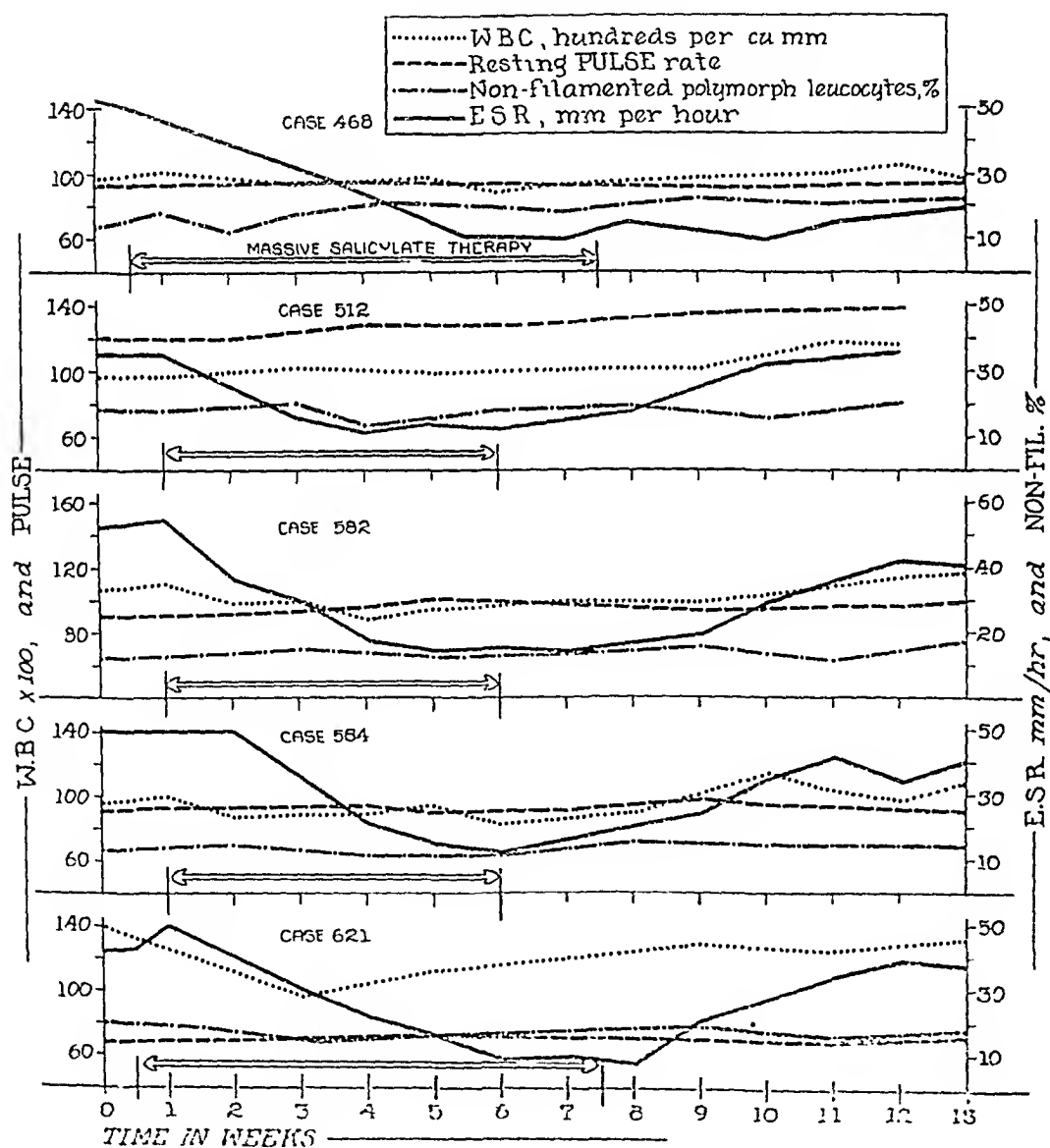


FIG. 2.—Clinical charts showing continued evidence of rheumatic activity, while the sedimentation rate is depressed by massive salicylate therapy.

is seen that the ESR in these cases reached normal limits, under the influence of massive salicylate therapy, while the white blood cell count still afforded evidence of continuing activity of the rheumatic process. The differential white blood cell count showed a shift to the left, or an abnormal number of non-filamented polymorphonuclear leukocytes, as additional evidence of a persisting inflammatory process. The resting pulse rate was elevated in 4 of the 5 cases, and in 2 of them the pulse rate showed a gradual rise over a period including that of the massive salicylate therapy. As to the clinical observations not charted, the following are relevant: (1) in no case was there a decrease in transverse diameter of the heart, or in intensity or transmission of murmurs during the period of salicylate therapy; (2) the vital capacity did not rise in any case during the period charted—in 1, Case 512, it fell from 0.8 to 0.5 liter; finally, no fever or polyarthritis was noted during the treatment, or any symptoms except those of salicylate toxicity.

In 4 of the 5 cases a definite rise in the ESR is seen to have occurred soon after the cessation of salicylate therapy.

Discussion. *The Comparative Sensitivity of the ESR and WBC Count.* Among the rheumatic patients studied during the past 5 years at these 2 institutions, 382 were observed during some phase of activity of the rheumatic process as indicated by laboratory tests. Of these, 328 patients were under observation until the quiescence of the infectious process. The laboratory data obtained in this group of patients indicate that the ESR, as used, was far more sensitive than the WBC count. Only in 6 cases, or less than 2%, did the WBC count remain above 8500 after the ESR had descended to the plateau level normal for that child. These findings on the comparative sensitivity of the ESR and WBC count in rheumatic fever agree with those of Ernestine.⁷ If we accept the finding of a shift to the left in the peripheral blood as having the same implication as leukocytosis these findings agree also with Rogatz²⁹

and with Struthers and Bacal.²¹ There is an apparent disagreement between these comparative data and those of Massell and Jones,¹⁵ and Wilson.²⁷ These authors found the ESR and WBC count of approximately equal sensitivity as indications of an inflammatory reaction, but this apparent disagreement is probably due to the standards used. Massell and Jones, and Wilson, considered as normal any corrected ESR of 0.38 mm. per minute (23 mm. per hour) or less, since that value is approximately the upper limit of normal for the population. There is, however, a wide range of individual variation in the ESR, and the normal values of some subjects may be as low as one-fifth the upper limit of normal for the entire population. In the case of a convalescing rheumatic patient seen for the first time in the acute stage of the disease, it is not possible to decide whether the patient's normal value has been reached when his ESR has fallen to the upper limit of normal for the population. Accordingly, in the author's laboratory, the ESR is considered normal for any given convalescent rheumatic when the falling curve of ESR *versus* time reaches a plateau. Used in this way, the ESR has been found to be far more sensitive than the WBC count as an indicator of persistent inflammation. This difference has been discussed because it considerably enhances the significance of the results reported here.

The Significance of the Data Presented. It should be noted that the clinical course of the 5 patients reported here is not typical of all those for whom massive salicylate therapy was instituted. Even among the patients selected for this study on the bases mentioned above it was found that in some the active rheumatic process began to subside shortly after the institution of massive salicylate therapy. In others, the depressing effect of salicylates on the peripheral WBC count, which has been described by other investigators,^{22, 27} sufficed to lower the count to the normal range, although there were other indications of continuing rheumatic activity.

The cases chosen for presentation were those in whom the clinical course and laboratory data permitted a demonstration of rheumatic activity during massive salicylate therapy.

This study constitutes no attempt to evaluate the effect of massive salicylate therapy in rheumatic carditis. Such an evaluation would involve prolonged study of patients in various categories of cardiac involvement. The purpose of this study has been to examine the hypothesis that massive salicylate therapy suppresses the inflammatory reaction in rheumatic fever, which is the rationale for this mode of treatment. The data reported here are inconsistent with this hypothesis, since they demonstrate that both general and specific evidences of rheumatic activity can be observed during massive salicylate therapy. The fact that such demonstration of continued rheumatic activity can be made at a time when the ESR is within normal limits as a result of such treatment, and the further demonstration that salicylates can lower the ESR in other states in the same degree as in rheumatic fever raises a question as to the significance of Coburn's observations on the basis of which the concept of massive salicylate therapy has been revived.

Summary and Conclusion. 1. Recently reported observations that large doses of salicylates may lower the erythrocyte sedimentation rate of non-rheumatic as well as of rheumatic patients have been confirmed.

2. The hypothesis that massive salicylate therapy suppresses the inflammatory reaction of the rheumatic patient has been tested by treating in this way patients in whom the rheumatic process is so active as to produce a prolonged leukocytosis. It has been found that, although the ESR is lowered to normal limits by such treatment, the leukocytosis may remain, although the latter is a much less sensitive indicator of inflammation. This finding is supported by a continued shift to the left in the differential blood count, and by specific signs of continued rheumatic activity, which were observed in the cases presented while the ESR was within normal limits as a result of salicylate treatment.

It is very doubtful, therefore, that massive salicylate therapy suppresses the inflammatory reaction of the rheumatic patient or that the lowering of the ESR in rheumatic patients so treated has the significance attributed to it by Coburn.

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CHANGES IN PERSONALITY APPRAISAL ASSOCIATED WITH A RESTRICTED INTAKE OF B VITAMINS AND PROTEIN

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PERSONALITY changes have been reported to be part of the syndrome of clinical B complex deficiencies.⁶ The symptoms of the "initial nervous syndrome,"¹³ described as being associated with pellagra and other deficiencies, are as follows: "hyperesthesia to all forms of sensation; increased psychomotor drive; increased emotional drive with a definite trend toward depression and apprehension, weariness and increased fatigability; headaches; sleeplessness. In general, these patients appear to have anxiety states with depressive features."

The development of the *Minnesota Multiphasic Personality Inventory* (MMPI) by Hathaway and McKinley⁴ permits more objective measurement of such symptoms. The possibility arises that it may aid in earlier clinical detection of psychopathology associated with certain nutritional deficiency diseases. The *Inventory* is based on the classification by the subjects of 550 "key" statements as "true," "false," or "cannot say." Scores are obtained by comparing the answers with those obtained from patients having known neurotic and psychotic aberrations (depression, hysteria, hypochondriasis, psychasthenia, schizophrenia, hypomania, psychopathic deviate, male-female interest and paranoia). Increase in scores beyond the range designated as normal (30-70) indicates a deviation in the direction of abnormal personality.

The purpose of the present communication is to describe the changes in personal-

ity appraisal scores (MMPI) which occurred while 7 young men subsisted on a diet containing restricted quantities of the B complex vitamins (including the "lesser-known" factors, i. e., pyridoxine, pantothenic acid, "folie acid" and biotin), and animal protein. Deviations toward the abnormal in certain categories, i. e., *hysteria*, *hypochondriasis* and *depression*, were definite when compared with the scores made by the same subjects during the "control period," and reverted to "normal" with equal definitiveness upon adequate supplementation with the nutrients which had been provided earlier in restricted quantities. These deviations appear to be similar to those reported in analogous investigations by Keys and associates.⁶ In addition, certain signs in other categories corroborated the changes which were indicated by the personality appraisal. These included the changed demeanor of the subjects that was apparent to all the observers, the marked contrast in demeanor between control and experimental subjects, a marked decrease in physical performance scores, and certain clinical signs, such as consistently high resting pulse rate and diastolic blood pressure.

Program. The subjects, environment, diet, etc., have been described in detail elsewhere.² In summary, 7 young male volunteers, aged 23 to 27, consumed a normal diet for 12 weeks, during which various measurements of physical and psychomotor performance were made in order to establish

normal or base line levels. Personality appraisals were made at the end of the normal diet period using the MMPI. Following this control period, an experimental diet which contained restricted quantities of B complex vitamins and animal protein was consumed by all 7 subjects for 5 weeks. The nutritive values of the normal and experimental diets are shown in Table 1, and a sample menu for the latter in Table 2.

TABLE 1.—NUTRITIONAL CONTENT OF THE NORMAL AND EXPERIMENTAL DIETS

<i>Nutrients</i>	<i>Normal diet</i>	<i>Experimental diet</i>
Calories	3170*	3300*
Protein (gm.)	70*	40
(l-Tryptophane) (mg.)	700-900	210-300
Calcium (gm.)	0 86*	0 20*
Phosphorus (gm.)	1 26*	0 58*
Iron (mg.)	15 50*	12 00*
Thiamine (mg.)	1 44	0 50
Riboflavin (mg.)	1 84	0 30
Niacin (mg.)	15 60	5 80
Biotin (mcg.)	44 00	19 00
<i>L. casei</i> factor (mcg.)	64 00	23 00
Pantothenic acid (mg.)	4 70	1 10
Pyridoxine (mg.)	1 70	1 10
Ascorbic acid (mg.)	105 00*	90 00*
Vitamin A (I.U.)	7400*	16,600*

* Calculated.

TABLE 2.—SAMPLE MENU OF EXPERIMENTAL DIET

<i>Breakfast</i>	<i>Dinner</i>
Applesauce	Baked hominy grits
Fried cornmeal mush	Hot beets
Fried salt pork	Perfection salad
Karo syrup with Maple	Plain cornmeal muffins
lene	Oleo
Oleo	Cranberry sauce
	Apple Betty
<i>Lunch</i>	<i>Bedtime</i>
Baked spaghetti casserole with corn muffin crumb topping	Cornmeal muffins
Green beans	Grape jelly
Carrots	Lemonade
Pickle relish	Sugar
Plain cornmeal muffins	
Oleo	
Pear halves	

NOTE: Normal diet consumed by all subjects the first 12 weeks; thereafter all subjects, both control and experimental, consumed experimental diet but former received supplements in quantities to equal or slightly exceed levels of nutrients found in normal diet. Calcium, phos-

phorus and iron levels of the experimental diet were increased to 0.9 gm., 1.1 gm., and 32 mg., respectively, by use of dicalcium phosphate and iron pyrophosphate. Ascorbic acid content of experimental diet was provided in part by synthetic lemon powder fortified with ascorbic acid. Vitamin A content of experimental diet was mostly in the form of beta-carotene.

At the end of the 5 weeks, 2 of the subjects were chosen as "controls" and received crystalline supplements of the B complex vitamins and protein in amounts to equal or exceed the levels found in the normal diet.* Three of remaining 5 subjects began an additive supplementation schedule at the end of 15 weeks, and the remaining 2 at 18 weeks. The general plan of supplementation differed for the 5 subjects. Within a relatively short period of time following experimental week 15, Subject E-3 received all the supplements given to the control subjects. Subject E-4 was similarly supplemented except that the lesser known B factors (pyridoxine, pantothenic acid, *L. casei* factor and biotin) were given some time after thiamine, protein, riboflavin and niacin. The remaining 3 subjects received the supplements according to a step-wise additive schedule. During experimental weeks 36 to 39, all subjects consumed a luxurious diet, plus supplements of crystalline nutrients and 10 gm. daily of high vitamin potency yeast. The schedule for control and experimental subjects was as follows:

Diet and Supplementation. Control subjects (C-1 and C-2): Control weeks 1 to 12—normal diet. Experimental weeks 1 to 5—experimental diet. Experimental weeks 6 to 35—experimental diet plus full supplementation. Experimental weeks 36 to 39—luxurious diet in quantities desired individually.

Experimental subjects (E-3, E-4, E-5, E-6 and E-7): Control weeks 1 to 12—normal diet. Experimental weeks 1 to 15 (E-3, E-4, E-5), 1 to 18 (E-6 and E-7)—experimental diet. Experimental weeks 16 to 35 (E-3, E-4, E-5), 19 to 35 (E-6 and E-7)—experimental diet plus additive supplementation with crystalline B vitamins and protein.

* The supplements were as follows: (1) 40 gm. animal protein (as 45 gm. calcium caseinate); (2) 0.7 gm. calcium as dicalcium phosphate; (3) 0.54 gm. phosphorus as dicalcium phosphate; (4) 20 mg. iron as iron pyrophosphate; (5) 666 I.U. vitamin D; (6) 1.2 mg. thiamine hydrochloride; (7) 1.5 mg. riboflavin; (8) 12 mg. nicotinamide; (9) 60 mcg. biotin; (10) 90 mcg. *L. casei* factor (folie acid); (11) 6 mg. pantothenic acid, half as racemic calcium pantothenate and half as dextro calcium pantothenate; (12) 300 mcg. para-aminobenzoic acid; (13) 3 mg. pyridoxine hydrochloride; (14) 0.5 gm. choline chloride as choline dihydrogen citrate.

Experimental weeks 36 to 39—luxurious diet in quantities desired individually.

Personality appraisal was made on 4 occasions during the experimental weeks 1 to 39. At the same time numerous other measurements were made weekly or bi-weekly, for the physical, psychomotor, clinical and biochemical aspects.

RESULTS. Significant changes occurred in the triad: hysteria, hypochondriasis and depression. Reference to Figure 1 shows that at the second appraisal, following some 15 weeks of the restricted intake of nutrients, a rise in score was obtained for all 5 experimental subjects in these 3

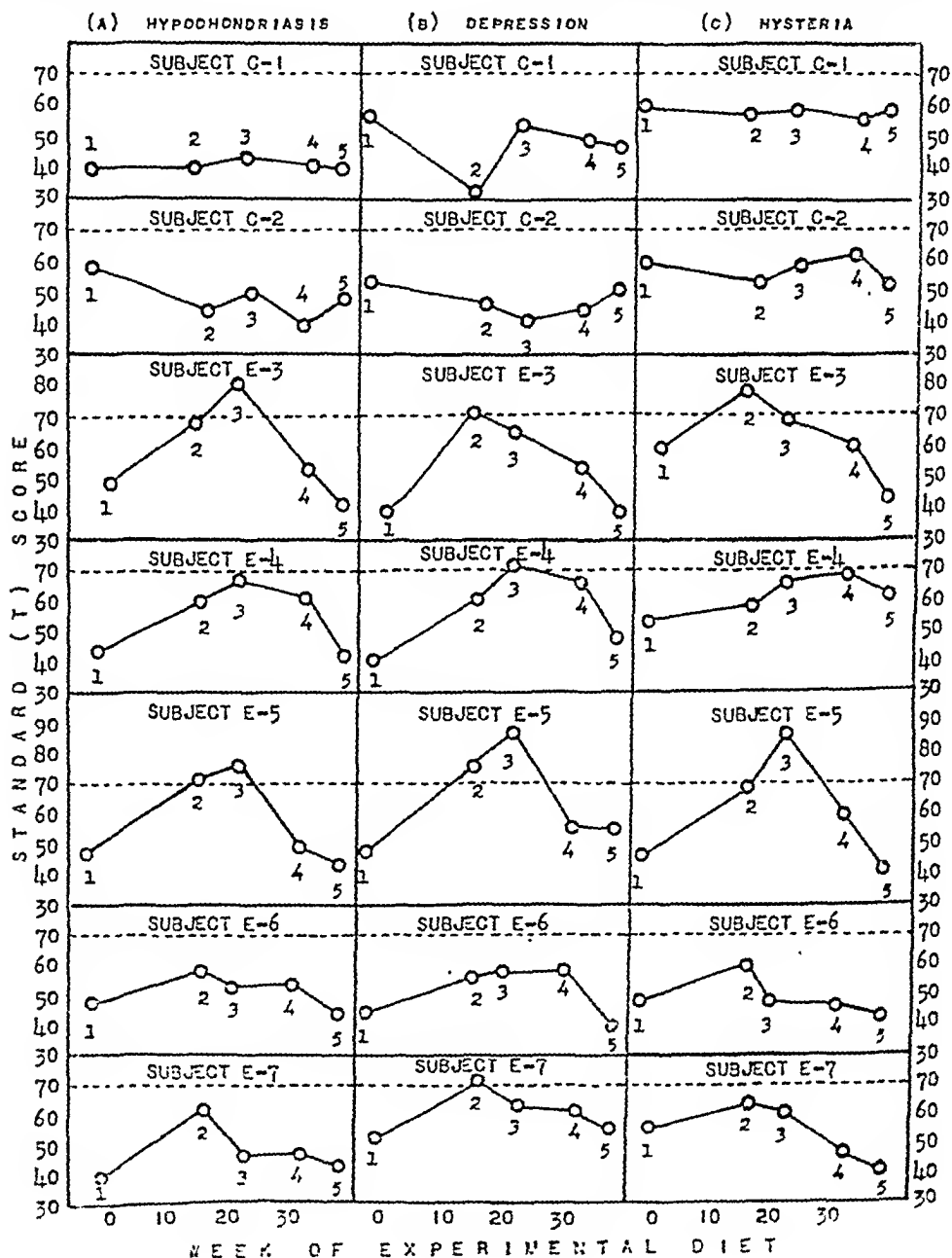


FIG. 1.—Scores in multiphasic test

personality categories, while the scores for the controls were either unchanged or decreased. Only a few of the increased scores made by the experimental subjects exceeded the normal range, however.

At the point of third appraisal, supple-

mentation with thiamine had been given to all subjects, protein to Subjects E-3, E-4 and E-5, and niacin and riboflavin to E-3. The times at which the various supplements were received are shown in Figures 1 and 2. Following supplementa-

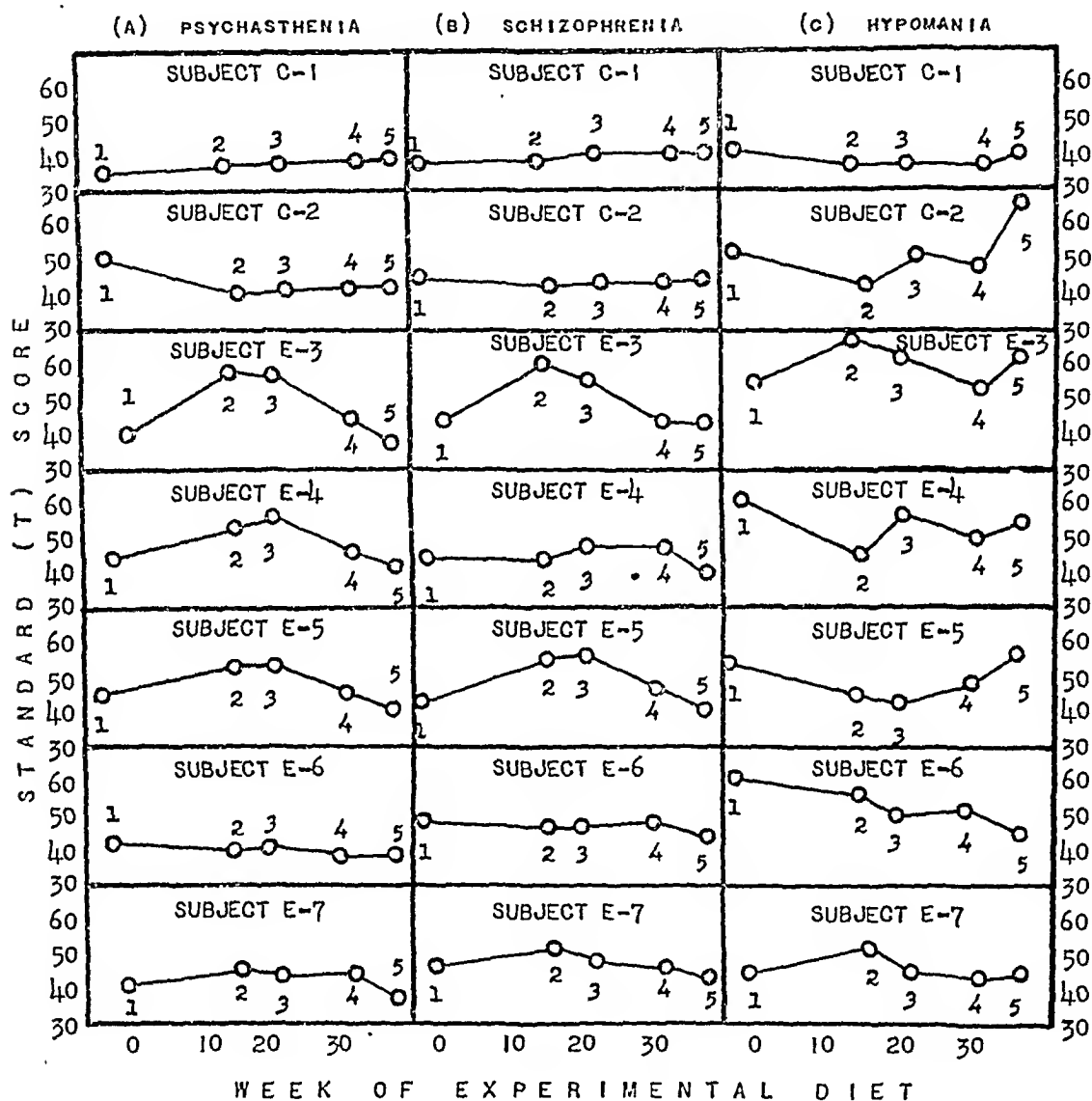


FIG. 2.—Scores in multiphasic test

Explanation of Figures 1 and 2: The normal range of scores on the multiphasic test is considered to be 30 to 70. The times at which the multiphasic tests were given are designated by the numerals 1, 2, 3, 4 and 5, corresponding to different dietary and supplementation régimes as follows: 1, Just before change from normal to experimental diet. 2, After approximately 15 weeks on experimental diet and just before supplementation of experimental subjects began. 3, Following 6 weeks of thiamine supplementation and 1 week of animal protein, nicotinamide and riboflavin to E-3; following 6 weeks of thiamine supplementation and 1 week of animal protein, supplementation to E-4 and E-5; and following 2 weeks of thiamine supplementation to E-6 and E-7. 4, Following 11 weeks supplementation with lesser-known B vitamins and 6 weeks of egg, meat and milk to E-3; following 6 weeks of egg, meat and milk, 6 weeks nicotinamide supplementation, 5 weeks riboflavin supplementation and 2 weeks lesser-known B vitamin supplementation to E-4; following 5 weeks nicotinamide and 4 weeks riboflavin supplementation to E-5; and following 5 weeks protein and nicotinamide and 4 weeks riboflavin supplementation to E-6 and E-7. 5, Following 2 to 3 weeks on a luxurious diet.

tion with thiamine, Subjects E-6 and E-7 showed slightly to moderately lowered scores representing lowered tendency to hysteria, depression and hypochondriasis, whereas the other 3 subjects presented in general higher scores, despite supplementation not only with thiamine, but also with the other nutrients described above.

At the time of the fourth test, the supplementation described above had been continued, and high excretion levels of those nutrients were found in the urine. By this time, other supplements had also been added so that all subjects were then receiving thiamine, protein, niacin and riboflavin, and Subjects E-3 and E-4 the lesser known B complex factors, in addition. Subjects E-5, E-6 and E-7 had not yet received the latter. At this point none of the scores exceeded the range of normal, although certain ones were still higher than those found originally. No marked difference in the improvement of scores was seen in those subjects not receiving the lesser known B complex factors as compared to those who did.

Return to approximately normal score levels for each individual was found at the time of the fifth and final appraisal which was carried out following 3 weeks of the luxurious diet.

Discussion. As mentioned previously, changes appeared only in the associated categories of depression, hysteria and hypochondriasis. Other categories including psychasthesia, schizophrenia, hypomania, psychopathic deviate, male-female interest and paranoia did not show decisive changes.

The described deviations in personality inventory substantiated the qualitative impressions of all observers concerned. Whereas the experimental subjects were languid, morose and occasionally irritable, it was necessary to request the control subjects to restrain their ebullient spirits in the interests of maintaining harmony in the group. Interesting alterations in resting pulse rates and diastolic pressures were found in the experimental subjects,

these being considerably higher than the corresponding readings taken during the control period, and returning to normal upon supplementation. Concurrent decreases in physical performance were observed with the increases in personality appraisal scores. Similar but not so decisive decrements were observed in psychomotor performance. The physical and psychomotor test results, described in detail elsewhere,² indicate that changes in those categories accompanied changes in personality appraisal described herein.

In the interpretation of results, we have contemplated the possibility that such factors as monotony of diet and the tedium of routine physical and psychomotor testing may have played important rôles in causing the deviations noted. This possibility is not excluded completely by the fact that the control subjects did not show similar changes, for knowledge concerning who were the control subjects and who were not, eventually became apparent to all of them—in spite of withholding this information from the subjects by using the same diet for all, placebos that were identical in appearance to the vitamin supplement capsules, and identical testing techniques for all. Knowledge that they were receiving supplements conceivably could have prevented the controls from undergoing personality appraisal changes similar to those found to occur in the experimental subjects. However, when the reversal of changes in the experimental subjects is interpreted, it is difficult to conceive of similar factors exerting an influence during that phase, for there was no way for the experimental subject to know if, when, or how he received supplements. These were added either directly to the food without the subjects' knowledge, or given by means of a tablet or capsule that was the same in appearance as the placebos. The only remaining explanation would appear to be that the changes in well-being and physical performance were paralleled, more or less, by return to normal scores on the personality appraisal test.

Summary. During a period of restricted intake of B complex vitamins and protein, 5 subjects showed changes in personality appraisal (*Minnesota Multiphasic Personality Inventory*) that were coincident with changes in other categories, notably physical and psychomotor performance and resting pulse rate and diastolic pressure. The changes occurred in the triad of hysteria, hypochondriasis and depression, but not in any of the other categories included in the Minnesota multiphasic test. Similar changes were absent in the control subjects. With supplementa-

tion, there occurred a beginning regression towards scores found originally during the initial normal diet period. This improvement progressed during the course of supplementation with thiamine, protein, nicotinamide, riboflavin and the lesser known B complex factors, and was concurrent with improvement in physical performance and feeling of well-being. Actual attainment of each subject's original "normal" scores occurred following a final 3 week period when a luxurious diet was fed.

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PROGRESS OF MEDICAL SCIENCE

DERMATOLOGY AND SYPHILOLOGY

UNDER THE CHARGE OF

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VIRUS PYOGEN AND VIRUS PYOGEN PHOTOSENSITIVITY RELATIONSHIPS IN CUTANEOUS DISEASE

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AN interesting trend of the present day is the growing appreciation of causal interplay in the field of infective agents. Primary and secondary infection, not alone in the field of the bacteria, but as between fungi and bacteria, and viruses and bacteria, is gradually attaining what is evidently a deserved recognition; and bacterial allergy as distinguished from simple bacterial infection is serving increasingly to explain or provide plausible theory for a range of manifestations much broader than those produced by simple infection alone. Moreover, allergic interplay is now taken to include interplay between bacterial and other types of allergic response. Foods ineite to exacerbatation and relapse of infections, infections bring about allergic responses to foods; and now infections ineite to allergic types of response to other infections, in sequences in which the primary offender is with difficulty identified, or perhaps has altogether disappeared in the commotion produced by the second organism participating in the infection-allergic sequence. Such infection-allergic sequences have been recognized in derma-

tology in the strepto-levurids for example, described by Darier, Ravaut, Ramel and their associates.¹⁶ They are with good reason suspected in the fungus-pyogen dermatoses included in the colloquial term, "athlete's foot" and the eczematoid eruptions of hands and feet. It is the purpose of this review to cover the groundwork of still another type of sensitization sequence, the "virus-pyogen sequence" as we shall call it, recognition of which is on the threshold, so to speak.

Such a concept is of use in explaining 2 painfully common phenomena in dermatologic practice: relapse and non-cure for which no gross external mechanism such as reëxposure to a contact allergen, for example, can be demonstrated. Inflammatory eruptions of varied origin, including industrial and contact dermatitis with "eczematoid" or "infectious eczematoid dermatitic" characteristics, and persistence after removal of the primary irritant or allergen; and the pyogen complicated flares of acne vulgaris, dermatophytosis, lupus erythematosus, and the eczema asthma hay-fever complex ("prurigo Be-

nier" and the so-called neurodermatitis disseminata) are cases in point. Without too much stretching, outright disease entities such as the varicelliform eruption of Kaposi can be grouped under these categories. Suspected virus diseases such as dermatitis herpetiformis, and the impetiginizing herpetic processes and bullous impetigoes seem less far apart; and drug eruptions very plausibly respond to interpretation by an approach to the Milian⁴⁷ formula of infection activation in which the drug merely stirs up a previously existing infection, or perhaps more currently, an infection allergy. The relationship between the sensitizing infection and

focal colony as at a tooth apex, disturbed, may act as a trigger for a wholesale herpetic outbreak or an exfoliative dermatitic "drug eruption." As isolated cases or small groups, these occurrences have now been recorded in the literature, with but scant attention to their etiologic integrative possibilities. Collecting them raises their impressive value and provides a basis for further study.

The following tabulation groups a number of virus infections (or suspected virus infections) in which pyogen correlates have and have not been suspected.

The virus pyogen sequence in variola-vaccinia has been interpreted historically

TABLE 1.—VIRUS INFECTIONS AND PYOGEN CORRELATES
Pyogen correlate or sequence suspected Pyogen correlate apparently absent

Vaccinia	Virus pneumonia
Variola	Virus hepatitis
Varicella-zoster	Encephalitis
Herpetic infections	Poliomyelitis
Herpes-impetigo (virus impetigo)	Ornithosis
Influenza	Mumps
Adult diarrhea, "food poisonings," etc.	Measles
Atypical diarrhea of infants	Rubeola
Nasorespiratory and bronchitic infections ("coryzal types")	Lymphogranuloma venereum
Apthous uveitis	Verruca vulgaris
Acute infectious gingivostomatitis	Molluscum contagiosum
Ectodermosis erosiva pluriorificialis	Waelsh urethritis
Triple syndrome of Behcet	
Erythema multiforme	
Dermatitis herpetiformis	
Pemphigus	
Catarrhal vulvovaginitis	

its consequence is at times reversible, and a pyogenic infection may seem to sensitize to a virus as in the Kaposi eruption, or the 2 may coexist, or, as we suspect more often, the virus paves the way for the pyogenic explosion, which follows it after a fairly well-defined incubation period or refractory phase, and completely overshadows the first offender. Moreover, it is not necessary that the sensitization be between agents on the same terrain, *e. g.*, the skin. The virus may be in the paranasal sinuses or the intestinal tract or distributed throughout the body in a general infection, and the primary or relapsing manifestations in a specialized skin structure such as the hair follicle. Or a small

as a coincidence by many observers, interest being absorbed by the corpuscular or granular body studies of Guarnieri and Negri in their application to variola by Pashen.⁵¹ The transmission of the disease by the bacteria-free fluids of the early vesicle quite overshadowed for a time the pyogen sequence. Arndt³ in the Dresden epidemic of 1918-1919, however, found streptococci and pneumococci in the blood. Hines³⁰ in the Chicago epidemic of 1922 found both the hemolytic and non-hemolytic streptococci in the blood. Ikeda³¹ in the excellent studies with Michelson⁴⁵ and Switzer⁶³ of the Minnesota endemic and epidemic smallpox, found that of 28 cases subjected to blood

culture, with the hemorrhagic form of the disease, 23 showed streptococci, 16 hemolytic and 7 non-hemolytic. Five were negative. In the discussion of Michelson and Ikeda's paper, Schamberg, whose experience with the disease was one of the largest, stated that though the fluid of the early variola vesicle is bacteria-free, by the 4th to the 6th day, streptococci are found both in the vesicles and in the blood. He recalled Councilman's statement that a patient does not die of smallpox *per se*, but of a streptococcic septicemia. Clinical observation of the course of variola does much to impress the belief that it is a syndrome of 2 infections, the viral stage including the appearance of the initial exanthem, and temperature rise, and the ensuing vesiculation, and the pyogenic invasion which produces the pustular manifestations, the secondary fever, the septicemic and hemorrhagic manifestations, abscesses, etc. Ikeda, however, insists from his study of the Minnesota material that the full-blown variola pustule is sterile, but the pustule with hyperemic reaction in the surrounding skin often yielded hemolytic streptococci.

What is evidently needed to amplify these suggestive observations is further study of pyogen susceptibility and pyogen flare reactions of persons with normal skins, following initial vaccination in variola epidemics, and of the behavior of the clinical pyogen-susceptibles with pustular acne, staphylodermias, etc., under similar circumstances.

The varicella-zoster relationship is still involved in controversy, chiefly as to the identity of the viral causes of the 2 diseases. We have been able to find little in the literature to suggest a virus-pyogen relationship in the clinical manifestations ascribed to the zoster virus, though Rosenow and Oftedal²⁴ thought they had reproduced zoster in animals by injecting streptococci isolated from various focal infections in patients suffering with zoster. Sund²⁵ found diplococci and short coccil chains in the Gasserian ganglion of the affected side in a case of herpes zoster

ophthalmicus. In contrast with the virus pyogen findings in herpes simplex, we have been unable to find any report of pyogenic invasion of the elementary zoster lesion. It would appear that a more intensive study of "complicated," i. e., gangrenous zoster, and secondarily impetiginized otic ganglion zoster (a not uncommon clinical complication) is desirable.

The impetiginization of herpes simplex lesions is a matter of common clinical observation but has had relatively little intensive bacteriologic study. Clinical experience also bears out the observation that impetiginization of herpetic lesions varies from individual to individual, and at different times in the life history of the same person. Geniculate ganglion herpes seems notably more frequently complicated by an early and rapid pyogen invasion, while the opposite seems to be the case in ophthalmic herpes. Possibly the soil on which the herpetic skin lesion appears is the determining factor. The ear and particularly the almost intertriginous retroauricular surface in ears set close to the skull, is a notorious haunt of streptococci as witness Mitchell's²⁶ study of the streptococcal dermatoses of the ear. Fenton's¹⁸ discussion of otic herpes zoster calls attention to the milder, eczematous type of eruptive manifestation in this disease, which may represent a pyogen invasion or sequence, and emphasizes the differential importance of pain in identifying the herpetic element in cases masked by the eczematous appearances. Thus it is more than suggested that one type of herpetic infection can underlie in certain cases a variety of clinical pictures ranging from the *porrigi scabida* or *impetigo scabida* of Alibert (the "French ear") to the *pityriasis streptoginea* of Haxthausen. Attention is also directed in these papers to the instrumentality of the draining ear of otitis media in providing a secondary inoculative source for impetiginous eczema of the canal and auricle. In cases in which no evidence of drum perforation past or present can

be found, the possibility of an activating otic herpes should not be lost sight of. Campbell¹² has commented on the symbiotic relation of virus and pyogen in the minor varieties of impetigo contagiosa and has even suggested that impetigo itself may be at bottom a virus disease.

The immunologic status of the herpes virus-pyogen involved skin also deserves more study. In 1934 Paeréau⁵⁰ reported the effect of a stock staphylococcus vaccine with anatoxin in reducing the size of zoster vesicles, preventing eczematization and relieving symptoms. Francois⁵¹ in 1936 used "antistaphylococcus vaccine" successfully in subcutaneous injection near the site of the zoster eruption, and Fouassier⁵² employed it both subcutaneously and intradermally. Godal⁵³ and Magrou a year later confirmed the reported favorable experience of the foregoing authors. Apparently no procedure for determining the grade of sensitivity of the zoster patient's skin to staphylococcus vaccine or toxoid was undertaken.

The Kaposi varicelliform eruption, most frequently observed as a complication of the eczematous phase of the eczema-asthma-hay-fever complex in our experience, is an explosive varioliform eruptive affair accompanied by high fever and sometimes septic symptoms, which has been studied earlier in relation to pyogen invasion and more recently, as virus culture techniques have improved, from the standpoint of the herpes virus. Jaquette, Convey and Pillsbury⁵⁴ briefly review the earlier literature since Juliusberg⁵⁵ in 1898 suggested that the characteristic umbilicate lesions were produced by *Staphylococcus aureus*. A number of the subsequent papers which recognized the presence of staphylococci rated them as incidental and not truly causal. Jaquette *et al.*, on the basis of clinical similarities, emphasize the possible primary etiologic agent as the vaccinia virus. Barton and Brumsting⁵⁶ classify a number of papers on the basis of staphylococcus, streptococcus and virus etiologic leanings. King⁵⁷ reported a case of Kaposi's varicelliform eruption which

began as herpes zoster. A number of authors since Freund⁵⁸ in 1934 reported the finding of Guarnieri bodies in the lesions of Kaposi varicelliform cases have attempted confirmation of his observation without success. The frequent presence of pyococci was acknowledged, but their significance contested.

In 1944, Blattner, Heys and Harrison,⁸ working on a case clinically reported by Lane and Herold,⁴⁰ identified a virus which they regarded as closely related to, or a strain of the herpes simplex virus, and discarded the previous theorization regarding the vaccinia virus. In 1945, Lynch and his co-workers⁴⁵ reported the finding of the virus of herpes simplex in a case of Kaposi varicelliform eruption. The source was not determined in this case, but 2 other cases followed herpes simplex in a parent of each of the children affected.

So far as the literature then indicates, the virus-pyogen relationship in this group of dermatoses ("eczema hepeticum" as Lynch and co-workers propose to call it) needs further study not only on the virus side but also on the typing, pathogenicity status and immunologic and allergic responses to the pyogens which have been identified. Jaquette *et al.* confirm Lynch *et al.*, and venture a step further in including the beta hemolytic streptococci and staphylococci they found, in the etiologic interplay.

The next group of possible virus-pyogen correlates on which a get-together is badly needed includes the following:

1. Rendu⁵³ and Fiessinger and Rendu:¹⁹ a syndrome characterized by simultaneous inflammation of all external mucous surfaces coëxistent with a varicelliform later purpuric eruption of all 4 extremities.

2. Klauder:³⁸ ectodermosis erosiva pluriorificialis.

3. Stevens - Johnson syndrome:⁵⁷ "a new eruptive fever associated with stomatitis and ophthalmia. See most recently Kove,³⁹ Stevens-Johnson syndrome.

4. Baader:⁴ dermatostomatitis.

5. Levine, Hoerr and Allanson:⁴⁴ vesicular pharyngitis and stomatitis.

6. Beheet:⁷ recurrent genito-oral aphthosis and uveitis with hypopyon.*

7. Franceschetti, Valerio and Babel:²³ using the above designation.

8. Ketzenellenbogen:⁵⁵ using the above designation.

9. Curth:¹⁵ using the above designation.

10. Scott, Steigman and Convey:⁵⁵ acute infectious gingivostomatitis.

11. Lever:⁴² severe erythema multiforme.

The clinical resemblances among these conditions are readily apparent to the dermatologist. Franceschetti and his co-workers²³ have well summarized some of the relations under a virus etiologic hypothesis as follows: Recurrent aphthous uveitis "is indeed an independent disease defined by the development of periodic attacks, by its complex and characteristic symptoms and by its resistance to treatment. . . . Although a virus explains in a fairly plausible way (since its existence cannot be proved with certainty, the inoculations having failed to produce the disease) the aphthae and uveitis, it is necessary to introduce another factor, which is the sensitization of the organism. This allergy, however, seems to be secondary, and not the initial cause of the disease." He then relates it to the allergic status of the ocular disorders associated with rheumatic states. Cavara¹³ and Adamantiadis¹ separately reported blood cultures of mildly pathogenic staphylococcus from the blood stream and Weve⁷⁰ felt that the articular process in erythema nodosum was a manifestation of an allergic state against the staphylococcus. Ageloff⁷ and Ginandes²⁷ separately report isolation of streptococci and staphylococci from the lesions. Gilbert⁷ thought the eye lesions metastatic and the patient the victim of a low-grade sepsis. Cavara and Adamantiadis in the Stevens-Johnson syndrome, believed that a virus made the body more susceptible to the staphylococcus.

Thus far, then, the negative holds the stage in this group so far as pyogen and virus etiology is concerned, but the application of better techniques on both sides may establish either or both causes, or an interrelation between the two. An allergic or sensitizing relation has already been suggested.

It is not the purpose of this summary to go in detail into the problem of virus etiology or influence in dermatitis herpetiformis and pemphigus whose clinical relations to erythema multiforme on the one hand, and to the known septicemic clinical forms of "pemphigus" (butcher's pemphigus, acute septic pemphigus of infancy) are familiar to dermatologists. For a good review of the latter group especially reference may be had to Lever's paper on severe erythema multiforme. There exist, however, as Callaway and Sternberg's¹¹ study of bacterial allergy in dermatitis herpetiformis illustrates, good reasons for suspecting that a bacterial allergic state is an important element (in their case pneumococcus Type VII) which underlies or participates in the cause of dermatitis herpetiformis. Urbach and his associates⁶⁷ support the virus concept for both dermatitis herpetiformis and pemphigus, while O'Leary and Welsh⁶⁹ and Welsh⁶⁵ have supported the streptococcal etiology of pemphigus. Until the virus work is elaborated and confirmed and the possibility of a filter-passing streptococcus derivative (see Rose now on poliomyelitis) studied, the problem of virus pyogen relationship in this group remains unsolved.

Virus-pyogen Correlation in the "Influenza" Nasorespiratory and Gastro-intestinal Virus Infection Field. This part of our summary is essentially a use of analogy (a not too strong form of argument in itself) to shed light on virus-pyogen relationships in the "exacerbative" group of dermatoses, which will be last considered.

The group of virus infections constituting so-called "influenza" has long been

* Attention should be called to the recent description of epidemic keratoconjunctivitis associated with epidemic dermatitis. O'Donovan and Michaelson, Brit. J. Ophthalm., 20, 193, 1946, and Editorial, Brit. Med. J., 145, January 25, 1947.

recognized as having a definite cutaneous eruptive phase which was well summarized by Derbandiker¹⁷ in 1933. From a survey of the literature and his own experience he described efflorescences ranging from roseola to varioliform pustular and erythema nodosum lesions associated with the febrile stage of the infection, and terminating promptly with the return of the temperature to normal. These "toxic erythemas" might be regarded as comparable to the roseolar phase of variola in the initial febrile stage. These are to be regarded as separate for discussion purposes from the sequential pyogenic manifestations which usually followed after an interval of several days, the virus infection as such. During the 1918 to 1920 influenzal years, Stokes and Callaway⁵⁸ in 1937 pointed out that there were numerous references to the sensitizing effect of the influenza or virus phase to subsequent invasion by pyococci. For example, Chickering and Park¹⁴ called attention to staphylococcal pneumonia as a frequent complication. Small and Stangl⁵⁶ isolated streptococci from most of their patients with pneumonia and found staphylococci and pneumococci in some instances. Staphylococcal empyema was a fairly common influenzal sequel in 1919; Ballin⁵ and Ransohoff⁵² noted it especially at the Cincinnati General Hospital, where pneumococci played little part. Levin⁴³ found empyema in 5%, otitis media in 12% and sinusitis in 10% of children with influenza. Keeler³⁶ pointed out that pyogenic otitis media follows mild as frequently as it does severe influenza. Abscess of the lung is rated by Fishberg²⁰ as especially common and serious as compared with other infections of the respiratory tract following influenza. Burgess and Gornly¹⁰ recognized in a more recent epidemic of mild influenza (1930) that there was a striking rise in the incidence of pneumonia and an increased tendency toward the fulminating type caused by *Staphylococcus aureus*, as in the 1918 epidemic.

The question as to whether the staphylo-

coccal diarrheas which appear in sub-epidemics during periods of influenzal prevalence are to be regarded as associates of the virus infection or merely coincidences is, of course, hardly settled. Attention has been drawn to them in an editorial,²¹ and Terrell and Owen⁶⁶ subsequently reported a 30-case epidemic. Jankelson and Massell³² believed the pyogenic lesions of the skin in 5 cases of ulcerative colitis contained the same organism as that obtained from the intestinal lesions. To quote Stokes and Callaway again, "It appears, then, that an induced sensitization to pyococci, whether of virus or of pyococcal systemic (gastro-intestinal) origin, is a fair presumptive sequel of epidemic intercurrent virus infection such as that which occurred during the year 1936 in the eastern part of the United States. During this year 134 instances were observed of an apparently direct relation of pustular flares to intercurrent infections such as the colds, grip, conventional influenza and the gastro-enteric type of infection. The incidence in female subjects slightly preponderated. One-third of the patients had infections of the upper part of the respiratory tract; one-half had gastro-intestinal infection, and one-fifth had grip. Relapses unexplained by other factors, such as diet, fatigue, negligence, ingestion of alcohol, nervous tension, contacts and climatic conditions, were observed, in order of frequency, in 81 patients with acne vulgaris and acneiform eruptions, in 17 with a mycotic-pyogenic-allergic dermatosis, in 12 with chronic extensive eczema (neurodermatitis), in 6 with pruritus ani et vulvæ, in 6 with dermatophytosis of the feet accompanied with dermatophytids and in a few with seborrheic, rosaceal or furunculoid eruptions, an eruption caused by stasis or by a drug, lupus erythematosus or cheilitis.

"It is notable as a first suggestion of the allergic character of this type of relapse that a marked trend toward familial pyogenic susceptibility was observed in the patients, as noted by Stokes and King⁶⁰ in their study of acne and seborrheic der-

matoses. This pyrogen-predisposed background appeared among patients with allergic eczema in 91%, with dermatophytosis in 84%, with acne in 75% and with pyogenic-mycotic-allergic dermatosis in 70%. A second suggestion of an allergic background for the phenomenon is the latent period, during which sensitization to the pyrogenic or pustule-producing agent might take place. In 69% of cases the outbreak began between the 7th and 11th day following the recognized onset of the general infection. Leipner²² observed a latent period of from 8 to 10 days preceding an epidemic outbreak of erythema multiforme in 50 of 50 boys in a school home, after mild coryza.

In interpreting these observations these authors call attention to the arguments in favor of an allergic background for the phenomenon, including the latent period of 7 to 11 days between the onset of the general infection and the appearance of the pyrogenic sequence recognizable in 69% of the cases observed. They further cite the early observations of Stokes and Cathcart²³ on the effect of nasorespiratory infection in causing a swing toward pustulation in previously uncomplicated and relatively mild exfoliative dermatitis, and of Stokes and Kulchar²⁴ on the infection-allergic interplay of both mycotic and pyrogenic infection in arsenical exfoliative dermatitis.

On the experimental side of the virus-pyrogen sequence, there is a notable paucity of studies. Glover²⁵ in his work with the influenza virus in ferrets, called attention to the rôle of streptococci in exploiting, so to speak, a virus infection, implying that the clinical picture was a summation of the effects of both infections. Stuart-Harris²⁶ comments on the notable lack of attention to the virus-pyrogen relationship which has marked current thinking, pointing particularly to *Staphylococcus aureus*.

The 3 most recent applications of the virus-pyrogen exacerbative sequence have concerned hemolytic-pyrogenic and mycotic pyrogen infections of the hands: prurigo Besnier (cutaneous phase of the eczema-

asthma-hay-fever complex and the production of photosensitivity. Stokes, Lee and Johnson²⁷ state that their physician and lay patients recognized the virus-pyrogen flares of the dermatitis of their hands, as well as did the authors themselves. Provocation of extensive idi was taken as evidence of the allergic basis of the flare. To quote: "Spreading erythema, increased edema, a shower of pustules locally, extension without change in morphology, local lymphangitis and lymphadenitis, sudden involvement of the predisposed flush areas (ears, center face, flexures (intertrigo), or a wholesale outbreak of a follicular papular patchy or diffusely confluent dermatitis, each or severally constitute the flare." Salomonides had to be used to control the occasional head to foot outbursts of pustules or a pemphigoid eruption. Nordin²⁸ and independently Boel²⁹ have apparently applied a concept of induced infection-allergy, to a hypo- or desensitizing treatment with vaccines of the secondary pyrogen invader factor in exacerbations produced by nasorespiratory infections, in the eczema phase of the eczema-asthma-hay-fever complex (prurigo Besnier). Stokes and Callaway (1937, described with case illustrations the development of light sensitivity following virus infections, and in a comment on the complexity of the situation involved, noted interrelations between light sensitivity and virus infection, light sensitivity and pyrogen flares with or without obvious relation to an outspoken nasorespiratory infection, and virus-pyrogen-nickel sensitivity. While they concede the mechanism to be obscure, they venture the suggestion that the light sensitivity in some cases may not be a true allergic affair but be the result of porphyrin absorption from the intestinal tract, where perhaps a perverted (pyrogen) flora follows the virus invasion. They invoke this concept also (a hypothetical shift in intestinal bacterial flora following virus infection) to explain in theory the exacerbation of pruritus ani and anal and inguinal intertriginous ecce-

mas following virus respiratory tract infections. It is in fact not inconceivable that catarrhal vulvovaginitis following respiratory virus infections from which micrococcus catarrhalis is recovered is an example of a virus-pyogen sequence.

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OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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THROAT MEDICATION: A SURVEY OF CURRENT TRENDS

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ALTHOUGH the throat is the site of the most common surgical operation in the world, it has been surprisingly free from that type of intensive physiologic investigation which, with some measure of success, has contributed to the improvement of nasal medication. As in the case of nasal medication, a judicious union between physiology and pharmacology, tempered by comprehensive bacteriologic studies and cemented by sane clinical judgment, can provide a firm foundation for rational throat medication. The more one examines the therapy of the abnormal throat, the more firmly does this thought impress itself.

For purposes of this discussion, the term "throat" is made to apply strictly to the mesopharynx—the region bounded posteriorly by the posterior pharyngeal wall; anteriorly by the base of the tongue and by the open space directed toward the mouth; laterally by the lateral pharyngeal walls; superiorly by the nasopharynx; and inferiorly by the larynx and upper pharyngeal end of the esophagus. Within the mesopharynx lie masses of lymphoid tissue, more or less symmetrically arranged to constitute Waldeyer's ring, which through their tendency to disease produce various acute and chronic inflammations and infections (tonsillitis, pharyngitis, "sore throat," Vincent's angina and lymphoid hyperplasia, to mention an important few). The manner of their treatment is twofold: local and systemic. A survey of current trends in throat medication for non-surgical conditions points to the importance of both approaches.

RATIONAL OR LOCAL THROAT MEDICATION. In recent years considerable doubt has been cast on the value of gargles in acute tonsillitis and acute pharyngitis. Although popular with the laity, the use of a gargle has no real therapeutic foundation since, as Richards²¹ points out, the very process of gargling necessitates an approximation of the posterior part of the tongue to the soft palate in order to prevent fluids from running into the larynx. Experiments²⁰ with methylene blue, designed to determine how efficient gargling may be, demonstrate that the dye cannot be seen beyond the third molar tooth and cannot reach the tonsillar areas. Painting the throat in acute infections, on the other hand, is only of psychic value.

According to MacGregor and Long,¹⁷ the efficacy of drugs administered orally as pastilles, lozenges or pills for local treatment of tonsillitis or pharyngitis depends largely on the direction of salivary flow which apparently varies in individuals and with posture. They conducted experiments with pastilles to estimate the amount of penicillin likely to reach affected areas at the back of the mouth. Of 50 subjects studied, some had had their tonsils removed and the rest had tonsils ranging in all degrees of size. The pastilles used were of the same base, shape and size as penicillin pastilles but contained 1% methylene blue instead of 500 units of penicillin. The pastille, for purposes of study, was placed in the mouth in the buccal fold between cheek and teeth and allowed to dissolve without

agitation. The degree of staining of the anterior pillars of the fauces, uvula and tonsils was considerable at the end of 5 minutes and much more at 15 minutes, although the tonsillar area was not as heavily stained as the other 2 sites. The pharynx, when reached, was only slightly stained.

These experiments appear to indicate that, with a gelatin base, dyes reach the tonsillar area to an extent sufficient to suggest that drugs administered in the same type of base should reach the tonsils in most cases. Lack of staining of the pharynx, however, in a large proportion of subjects suggests that any attempt to treat pharyngitis with drugs contained in pastilles or lozenges is often doomed to failure. Flow of saliva at the back of the mouth and the swallowing mechanism appear to be such that saliva does not bathe this region as effectively as the oral cavity.

Arnett¹ believes that drugs incorporated in paraffin are slowly released into the saliva when chewed. During the process of chewing and swallowing they come into intimate contact with the gingiva, the pharynx and the esophagus. In order to determine the extent and degree of mucosal staining produced by the incorporation of methylene blue and gentian violet, observations were made on 13 subjects. While it was found that dyes stained the tongue and gingival margins deeply and the buccal mucosa moderately, the tonsils and the posterior pharyngeal structures were usually unstained when the patient remained in an upright position; however, when the subject chewed and swallowed while in a recumbent position, with head lower than shoulders, the tonsils and posterior pharyngeal tissues usually became stained.

Vollum and Wilson²² describe an outbreak of scarlet fever due to *Streptococcus pyogenes*, Type II, in a residential preparatory school for boys and an outbreak of sore throat accompanied by cases of scarlet fever due to Type I streptococci in a residential public school for girls. Treat-

ment of healthy and of convalescent carriers with 6 to 12 lozenges (containing 0.5 gm. sulfapyridine and 0.5 gm. sulfathiazole) a day for 5 to 7 days apparently had no effect in clearing the infecting type of streptococcus from the throat as compared with control carriers receiving either a spray or no treatment. Prophylactic treatment of healthy, non-infected individuals with 6 lozenges daily had no apparent effect in preventing streptococcal infection of the throat. Observations made on persons sucking methylene blue tablets demonstrated that only a fraction of the dye was deposited on the tonsils and none on the posterior pharyngeal wall. The authors, therefore, conclude that neither for prophylaxis nor for cure of streptococcal infection of the throat are lozenges containing sulfonamides likely to be valuable in clinical practice.

A more optimistic note is struck by Rosenthal²⁵ who finds that penicillin lozenge medication elicits a response superior to that obtainable with a triple dose of penicillin by injection. He finds that a gelatinous throat lozenge gives excellent results in follicular tonsillitis and ulcerous Vincent's angina. The patient is admonished to permit the lozenge to dissolve slowly on the tongue; the medication goes into solution within approximately 15 minutes when the lesions are bathed in a buffered solution of penicillin (2500 units). One lozenge is administered hourly. It is also reported that a chewing wafer of sulfonamide mixture gives excellent results in cases of severe pharyngitis and mild forms of tonsillitis. The patient chews the wafer as he would gum. The inflammatory process usually resolves within 2 or 3 days. In the opinion of Fox and Kesel⁷ and their associates, effective topical application of sulfonamide drugs to diseased or injured oropharyngeal tissues has been difficult, mainly because mechanical factors prevent the maintenance of a satisfactory concentration of the drug. The smooth oral mucosa is continually washed by saliva and does not lend itself favorably to treatment by

powders, ointments or solutions. From the standpoint of minimal systemic toxicity and minimal local antibacterial potency, they maintain that sulfathiazole in chewing gum seems to be the preferable local chemotherapy for the infections of pharyngeal and oral mucosa which are susceptible to sulfonamide compounds. Best clinical results are claimed in conditions of the pharynx and mouth in which the beta hemolytic streptococcus is the preponderant etiologic organism. In 52 cases of acute lymphoid pharyngitis and follicular tonsillitis, 72% showed a decided decrease in the total count within 48 hours, along with the complete disappearance of the beta streptococci in the cultures.

It has been asserted by Fantus⁶ that a hydrogen ion concentration near that which is normal for the mucous membrane is of even greater importance for applications to the mucous membranes than is isotonicity. So far as concerns the pH values of local medicaments, valid therapeutic conclusions have been drawn in a variety of clinical fields from measurements of the hydrogen ion levels of various secretions found in their original positions on underlying mucous membrane and tissue surfaces. Fabricant⁵ finds the normal physiologic range of values for the pH of the mucous membrane of the throat in a large group of men and women with clinically normal throats to be from 4.9 to 8. For 54.8% of the subjects the values were entirely within the acid range; for 7.8%, entirely within the alkaline range, and for 37.4% they fell within a slightly acid, slightly alkaline range of fluctuations. From these observations it is apparent that the normal human throat may be either acid or slightly alkaline. The claims advanced by some pharmaceutical manufacturers that their particular varieties of local throat medicaments "neutralize excess acidity in the mouth and throat" and that therefore they are superior because of this quality can indeed be challenged when it becomes clear that the pH of the mucous membranes of the

throat normally is, for the most part, within an acid range.

Results of treatment of 69 patients with acute pharyngeal infections by insufflation of sulfanilamide powder are reported by Goldman and Kiesewetter.⁹ The powder was insufflated once a day early in the series and later twice a day. Fifty-four patients with similar conditions were treated by other currently accepted standard methods. The average time required for clinical cure was 1.8 days shorter in patients with acute tonsillitis treated with sulfanilamide powder than in the controls, and 1.7 days shorter in patients with Vincent's ulcerative tonsillitis. The insufflations appeared effective in 9 patients with acute pharyngitis, but this group was deemed too small for comment. About 5 gr. of the sulfanilamide powder was employed at each insufflation. Blood examinations of 16 patients revealed no detectable amount of sulfanilamide. Freeman⁸ advocates the local use of sulfathiazole powder for acute pharyngeal infections. Sulfathiazole powder is applied until it thickly cakes the involved areas. It is claimed the method rapidly produces subjective and objective relief and materially shortens the course of the disease. In the experience of Hollender,¹⁰ sulfathiazole powder treatment, as compared with other topical remedies for pharyngitis, gives every indication of being effective in relieving the symptoms more promptly and in shortening the course of the disease. In the chronic cases a number of applications may be necessary and these should be given at intervals of several days.

Struble³¹ maintains that in most cases acute pharyngitis responds well to the intelligent use of time-tried methods of treatment, such as rest in bed, irrigations of the throat with hot, isotonic solution of sodium chloride, and carefully controlled treatment with sulfonamide compounds. It has been his custom to continue using these methods and to administer penicillin intramuscularly only when other means of therapy appear to be inadequate.

One method of irrigating the throat

involves supplying irrigating fluid from a container held slightly above the patient's head; the fluid is allowed to run over the tonsils and posterior pharyngeal wall. Syringes and modifications of a douching apparatus can likewise be employed in irrigations of the throat. Marcotte¹⁹ studied 29 patients with symptoms of granular pharyngitis, all of whom presented the typical nodules of hypertrophied lymphoid tissue distributed in varying amounts over the pharyngeal mucosa. Treatment locally consisted of cauterization with a 50% silver nitrate solution or destruction by means of electrocoagulation.

THE USE OF SULFONAMIDES AND PENICILLIN. In upper respiratory tract infections the incidence of hemolytic streptococcus in cultures from the nasopharynx varies from year to year. In army and civilian hospitals in New York City and its environs, the incidence during the winter and spring of 1943-44 was 35.4%, as compared with 5.8% for the previous year. There was also an accompanying increase of acute follicular tonsillitis and pharyngitis, often complicated by peritonsillar abscess, pneumonia and empyema. Owing to the increasing seriousness of these infections, Plummer²² and his associates made a clinical and bacteriologic study of the effect of penicillin (28 cases), sulfadiazine (11 cases), and no specific therapy (6 cases) on 45 patients acutely ill with tonsillitis or pharyngitis due to Group A (Lancefield) hemolytic streptococcus. Nine patients received intramuscular injections of penicillin for 24 hours. Peritonsillar abscess was a complication in 2 of these patients. After 24 hours of treatment, cultures were negative for hemolytic streptococcus in 8 cases, but after penicillin was discontinued the organisms reappeared in nasopharyngeal cultures. Of 9 patients who received penicillin for 3 to 4 days, there was bacteriologic and clinical relapse in 4 soon after the discontinuance of penicillin. In these 4 individuals large numbers of hemolytic streptococci were found in nasopharyngeal cultures 48 hours after penicillin was

stopped and concomitantly a return of pharyngeal swelling, redness and exudate in 2 of the patients as pronounced as at the onset. During the course of sulfadiazine therapy, the hemolytic streptococci in the nasopharynx were reduced in number, but in only 1 of the 8 cases showing many hemolytic streptococci in the initial culture did these organisms disappear, even temporarily; in all 8 patients they were present in the cultures in large numbers soon after the discontinuance of sulfadiazine. Thus, adequate sulfadiazine therapy in acute streptococcus tonsillitis and nasopharyngitis does not always prevent the patient from becoming a carrier. The authors also had several patients with acute tonsillitis who developed peritonsillar abscess or pneumonia and empyema while taking sulfadiazine in adequate and comprehensive amounts.

While evaluating sulfadiazine and penicillin therapy in tonsillitis, nasopharyngitis and scarlet fever on the basis of observations on 210 young men, Spink²⁹ and his associates studied approximately 2000 cultures from the nose and throat. As a control, neither sulfadiazine nor penicillin was used in the treatment of 102 patients with acute tonsillitis or nasopharyngitis. The utilization of sulfadiazine did not shorten the clinical course of tonsillitis and did not eradicate hemolytic streptococci from the pharynx. However, in very ill patients the severity of the disease appeared to diminish more rapidly than in untreated controls. Total doses of 200,000 units of penicillin administered intramuscularly to patients with severe tonsillitis and nasopharyngitis reduced the severity, and in some instances, apparently shortened the duration of the disease. It was necessary to administer doses of 500,000 to 1,000,000 units of penicillin before eliminating hemolytic streptococci from cultures of throat material for more than a short period. Clinical relapses following the administration of penicillin took place frequently and apparently were related to the reappearance of hemolytic streptococci in the

throat. In the treatment of tonsillitis, penicillin followed by sulfadiazine apparently possessed no advantage over penicillin alone.

In a study of the effect of sulfanilamide in the treatment of sore throat due to hemolytic streptococci, Rhoads and Afremow²⁴ made observations on 31 patients treated with sulfanilamide and 36 controls treated under similar conditions but without sulfanilamide. They concluded that in the average uncomplicated case of tonsillitis or pharyngitis due to hemolytic streptococci, the advisability of its routine use is questionable. In support of this point of view, Kernan,¹⁴ Richards,²³ and Hughes¹² all question the oral use of sulfonamide compounds in acute uncomplicated diseases of the pharynx. Smith²⁵ finds penicillin of definite value in the treatment of acute follicular tonsillitis. The clinical response was rapid and it was necessary to administer the drug for from 5 to 7 days. In his series of cases administering the drug by intramuscular injection gave an advantage over medication by mouth. Lierle and Paul¹⁶ gave oral penicillin to 36 cases of acute pharyngitis and acute tonsillitis. All but 6 showed noticeable improvement within 24 to 48 hours. Six who failed to respond after 48 hours were placed on sulfonamide therapy; the entire number improved immediately.

A comparative study of untreated cases and cases treated with sulfathiazole and sulfadiazine is described by Clodfelter² who only selected severe cases of acute tonsillitis, the type frequently referred to as "strep throats." The 400 cases selected for study were chosen from over 3000 cases of acute upper respiratory tract infections of such severity as to require hospitalization. Of 175 patients treated with large doses of sulfonamides, 41 ran a course similar to that of untreated patients and were discharged the 5th or 6th day. A secondary rise in temperature occurred in 134 of the treated patients; most of these were discharged the 10th day, the average number of hospital days

being 9.7. Clodfelter concludes that use of sulfonamides in severe cases of acute tonsillitis results in a prompt drop in temperature with some relief of symptoms. However, there is usually a secondary rise in temperature at the time untreated patients are being discharged, after an average of 5.3 days of hospitalization. Further, treated patients did not feel as well on the 10th day as untreated patients did on the 5th. Other findings strongly suggest that the use of sulfonamides in the treatment of acute "strep" tonsillitis is not only without benefit but is actually detrimental.

In a study to evaluate the rôle of penicillin in the treatment of acute sore throat, Davison³ observed 28 cases of acute sore throat. The dose of penicillin employed was 20,000 units every 3 hours day and night by intramuscular injection. No gargles, irrigations, analgesics or antipyretics were utilized. In all but 2 patients the tonsils were present, and in all patients there was tonsillar exudate, edema and diffuse inflammation of the tonsils and pharyngeal wall. In the 2 men who had had previous tonsillectomies, a diffuse follicular pharyngitis was found. The average total dose of penicillin in 27 cases of acute sore throat was 360,000 units over 54 hours. There was 1 relapse, in which recovery occurred without further penicillin. One case did not respond until sulfadiazine replaced penicillin as the treatment. No complications occurred, either during or after treatment.

Numerous reports appearing in the medical and dental literature indicate that penicillin is an outstanding therapy for the treatment of Vincent's fusospirochetal infection of the throat and mouth. Shallenberger²⁷ and his associates found that the local application of penicillin solution, 250 to 500 units per cc. of physiologic saline, administered 4 times daily was highly effective in Vincent's angina. Negative smears were obtained in much shorter time than with sulfadiazine lozenges or oxidizing agents such as silver nitrate or oxyphenarsine hydrochloride.

Hopp¹¹ treated 25 patients for Vincent's angina with sodium penicillin in gelatin capsules, 10,000 units each, 1 being given every 2 hours for 10 doses. Cure was obtained in 24 hours. Similarly, 37 patients were treated for acute follicular tonsillitis and cure was obtained in 3 to 5 days. Schwartz²⁶ found good response to intramuscular injections of penicillin in Vincent's angina. Joseph¹³ also reported excellent results with penicillin therapy in a series of patients with Vincent's ulcers of the tonsils. Eighteen patients received 100,000 units of penicillin parenterally each day in the form of 2 injections. In all 18 patients the lesions cleared completely within 7 days. Manson and Craig¹⁸ advocate the treatment of Vincent's angina with sulfathiazole. The treatment consists of medication with a 0.5 gm. sulfathiazole tablet, dissolved on the tongue, and given every 2 hours during the day and every 4 hours at night.

While bismuth is now seldom employed in the treatment of Vincent's angina, for a number of years various observers have advocated the parenteral use of bismuth preparations in the treatment of acute tonsillitis. Thus, Monteiro²¹ advises injection of a bismuth compound for follicular, parenchymatous and catarrhal types of tonsillitis. Lewis¹⁵ administers a bismuth salicylate in oil preparation intramuscularly, and Stovin³⁰ recommends for acute tonsillitis the administration of the bismuth salt of heptadienecarboxylic acid in suppository form.

That penicillin should be given together with antitoxin in all cases of severe pharyngeal or nasopharyngeal diphtheria is concluded by Dodds⁴ from a comparison of results in 2 series of patients treated respectively with antitoxin alone and combined with penicillin. Penicillin dosage was usually 100,000 units in 24 hours, given intramuscularly in divided doses. The author states that although penicillin therapy did not appear to affect the rate of clearance of the membrane, it did apparently reduce the incidence of complications. In the 13 cases treated with the usual doses of antitoxin plus penicillin, 9 cases escaped paralysis, while only 3 developed clinical myocardial involvement. In the 14 cases treated with antitoxin alone, only 4 patients escaped paralysis while 9 developed clinical myocardial involvement. One death from early myocardial failure occurred in each group.

In conclusion, it can be stated unequivocally that the sulfonamides and penicillin enjoy a prominent position in the ranks of throat medication. Their uses, however, are limited by the development of allergic reactions, by the sensitiveness of patients to these drugs, by the acquisition of "sulfonamide-resistance" and "penicillin-resistance" states, and by their ability to mask symptoms. Their abuses, on the other hand, are encouraged by promiscuity and by lack of intelligence in prescribing for patients with throat ailments.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF FEBRUARY 18, 1947

Factors in the Control of Capillary and Venous Pressure Demonstrated by a Schema. H. C. BAZETT, M.D. (Dept. of Physiol., Univ. of Penna.). A schema is demonstrated which has a circular flow of fluid. By a device originally described by Krogh the stroke volume may be measured. The pump is driven by water derived from a reservoir entering a vessel and compressing a rubber balloon. Control is attained by solenoid valves operated through cams driven by an electric clock motor. The pulse rate remains constant but can be altered by changing the cams. Similarly the ratio of systole to the cycle may be varied as desired. Simulated arteriolar resistances consist of 8 hypodermic needles arranged in parallel so that any number from 1 to 8 may be used. The arteriolar resistance is thus quantitatively known. Venous resistances on the other side of the "capillary" can be regulated and their values may be calculated according to the rate of flow and observed pressure gradients.

The simulated capillaries may be connected at will with fluid reservoirs intended to simulate tissue fluid. When so connected fluid enters the vascular bed from these reservoirs, if the capillary pressure is below that of the reservoir, and leaves the vascular bed for the reservoir, when the reverse relationship holds.

It can be shown that capillary pressure cannot be maintained constant when arteriolar resistance is altered, unless venous resistance is also altered in such a way as to maintain a constant ratio of arteriolar and venous resistances. The actual level of venous pressure attained during flow depends on the basic pressure to which the whole system is filled (direct), the total resistance in the circuit (inverse),

and the rate of flow (inverse.) Fluid interchange can modify the basic filling pressure during flow.

Histologic Changes Produced by 2,4-Dimethyl-3-hydroxy-5-hydroxymethylpyridine, an Analogue of Pyridoxine. CHARLES W. MUSHETT, PH.D., ROBERT B. STEBBINS and MARY N. BARTON (Merek Institute for Therapeutic Research, Rahway, N. J.). The administration of 2,4-dimethyl-3-hydroxy-5-hydroxymethylpyridine (desoxypyridoxine) to a variety of laboratory animals, including the chick, has resulted in atrophy and degeneration in the hematopoietic organs, particularly in those of the lymphoid series. These changes, as a rule, were reflected in the peripheral blood picture. Atrophy in the spleen was accompanied by an apparent increase in the reticular and trabecular elements. In the thymus Hassall's corpuscles, as well as the lymphoid tissue, were involved. Further experimentation is indicated before a statement can be made regarding the potential usefulness of this compound in the treatment of tumors of the lymphoid system. Examination of the adrenal glands of treated animals revealed a decrease in Sudanophilic material, even when these glands were larger than normal. Desoxypyridoxine exaggerated certain deficiency symptoms in puppies on a pyridoxine-free diet, but caused a delay in the appearance of other symptoms. Hyperirritability and convulsions, similar to those observed in pyridoxine deficient animals, could be elicited by a single large dose of the vitamin analogue.

Electromyographic Studies of Human Poliomyelitis. ROBERT HODES, PH.D.

(Johnson Foundation and Dept. of Physiological Medicine, Univ. of Penna.). Fourteen patients, 7 to 16 years of age, were examined electromyographically. Onset of acute poliomyelitis had occurred 4.5 to 11.5 years previously.

The electromyographic technique consisted of stimulating percutaneously the nerves supplying the muscles of the forearm, hand, leg and foot, and recording the maximal muscle potentials with surface electrodes. The muscle potentials were amplified by a 3-stage, condenser-coupled amplifier and photographed on moving bromide paper from a 5 inch cathode ray tube.

The response of the muscles of poliomyelitis patients to brief repetitive nerve stimulation is abnormal. The potential evoked by the first of a train of stimuli is greater in amplitude and duration than any of the succeeding spikes produced by identical stimuli to the motor nerve. Such an abnormal electromyogram results from failure of some muscle fibers to respond during the course of tetanic excitation. Single motor unit studies show that some of the component muscle fibers of the unit may fail. In addition, entire motor units may drop out of action during repetitive nerve action.

The failure of some muscle fibers to respond is due, at least in part, to an abnormality at the neuromyal junction which results from the disease process. The possibilities of impaired nerve and muscle function are not excluded.

Prostigmine (1 to 1.5 mg. intramuscularly) restores the electromyogram towards normal (6 patients). The effects of this drug should be studied in a larger series of patients for its possible therapeutic use as a partial restorative of muscle power and as a deterrent to fatigue.

Our experiments demonstrate the existence of peripheral defects in poliomyelitis

and require that current concepts of its pathology be broadened to include not only the central nervous system but also those peripheral structures whose activity bring about muscular contraction.

A Study of the Factors Controlling the Differentiation of Mauthner's Cell in Amblystoma. JEAN PIATT, PH.D. (Dept. of Anatomy, Univ. of Penna.). Mauthner's cell in amblystoma occurs at the level of the eighth nerve roots and is in close anatomic and functional relationship with these roots, also the seventh and tenth lateral-line roots. The consistent association between this giant neuron and the vestibular and lateral-line roots suggests the possibility that this relationship may be one of cause and effect, *i. e.*, Mauthner's cell may differentiate under the influence of the eighth or lateral-line nerve roots. A greatly varied series of experiments was carried out on amblystoma punctatum embryos to test this thesis.

Mauthner's cell failed to differentiate in about one-third of those cases in which the eighth roots were prevented from developing. A supernumerary Mauthner's cell developed in a few cases in which experimentally induced ectopic seventh, tenth lateral-line and eighth roots entered the brain at heterotopic levels, more frequently in association with the eighth. Neither consistent nor positive results accrued in many cases but the data, on the whole, indicate that the differentiation of Mauthner's cell is influenced to some extent by the presence of eighth, chiefly, and perhaps also seventh and tenth lateral-line nerve roots. A total of 212 experimental animals was individually studied and form the basis for these tentative conclusions.

BOOK REVIEWS AND NOTICES

ELECTROCARDIOGRAPHY IN PRACTICE. By ASHTON GRAYBIEL, M.D., CAPT., MC, USNR, Co-ordinator of Research, U. S. Naval School of Aviation Medicine, Pensacola, Fla.; and PAUL D. WHITE, M.D., Lecturer in Medicine, Harvard Medical School, Physician, Massachusetts General Hospital. 2nd ed. Pp. 458; 323 ills. Philadelphia and London: W. B. Saunders, 1946. Price, \$7.00.

THE authors state that this edition was made necessary primarily because of recent advances in the science of clinical electrocardiography. Much material on precordial leads has been added. The general format and style have not been altered. The method of presentation used throughout the book is to introduce each subject with a brief discussion of pertinent electrocardiographic characteristics and then demonstrate them by means of case reports. In these the interpretation of the electrocardiogram is discussed prior to the presentation of clinical data. The last step is correlation of the 2. The book offers an excellent introduction to electrocardiography because the authors know their subject, the discussion is simple, points of controversy are clearly stated, and the field of clinical electrocardiography is well covered. C. W.

RENAL HYPERTENSION. By EDUARDO BRAUN-MENENDEZ, JUAN CARLOS FASCILOLO, LUIS F. LELOIH, JUAN M. MUNOZ and ALBERTO C. TAQUINI, Institute of Physiology, Faculty of Medical Sciences and Institute of Cardiology, V. F. Grego Foundation, Buenos Aires, Argentina. Translated by Lewis Dexter. Pp. 441; 93 ills. Springfield, Ill.: C. C. Thomas, 1946. Price, \$6.75.

THE authors' intention is to present a complete and balanced review of the renal aspects of hypertension, experimental and clinical. Their own contributions to knowledge of experimental hypertension more than justify the inclusion of a preponderance of their own data. However, nothing can justify evident emotional bias in their discussions of other investigations and investigators.

The short section on clinical hypertension

is obviously second-hand and carries none of the conviction of the experimental. It is therefore not recommended to clinicians. On the other hand, the book will be useful to investigators, even though it is a disappointment to those who had hoped for a balanced treatment of this important subject. The Reviewer still thinks that this excellent group of investigators is capable of giving one. The Bibliography is thorough. The publisher has shown his usual attention to the niceties of bookmaking. I. P.

RECENT ADVANCES IN ENDOCRINOLOGY. By A. T. CAMERON, M.D., M.A. Pp. 415; 76 ills. Philadelphia: Blakiston, 1946. Price, \$5.00.

THE various endocrine glands of the body are considered in the light of chemistry, physiology, pathology and clinical manifestations and treatment of endocrine disturbances. Much emphasis is placed on therapy. Pathologic aspects are short and sometimes incomplete. Clinical manifestations of alterations in the pituitary, thyroid, parathyroid, adrenals, islets of Langerhans, and reproductive glands are given thorough consideration. There is a separate short discussion of gastro-intestinal hormones, pineal gland, rennin and antihormones. The book is especially valuable to the clinician because of its lengthy diagnostic and therapeutic aspects. I. Z.

GENERAL BIOLOGY. By WILLIAM C. BEAVER, Professor of Biology, Wittenberg College, Springfield, Ohio. 3rd ed. Pp. 820; 325 ills. St. Louis: C. V. Mosby, 1946. Price, \$4.75.

THE text material is presented in 4 parts. Part I deals with protoplasm and the general morphology and physiology of plant and animal cells. Part II includes a survey of the animal kingdom and the physiology of the organ systems of man from a phylogenetic approach. A similar procedure is followed for the plant kingdom in Part III. Part IV discusses the interdependence of living organisms, ecology, paleontology, heredity, evolution and biochemical and biophysical phenomena, with discussions of biology in relation to medicine, economics

and so on, and a very brief review of the history of biology. A 5th section includes a list of combining forms and a glossary. The book is well indexed.

The phylogenetic arrangement of the physiology of the organ systems leads to repetition and the details of the text tend to conceal the general ideas and concepts of biology which the non-specializing student should carry away from a general course.

After reading this text through, one gets the impression of having gleaned a smattering of facts about all fields of biology but no real understanding of any. M. McC.

MEDICAL EDUCATION AND THE CHANGING ORDER. By RAYMOND B. ALLEN, Executive Dean, Colleges of Dentistry, Medicine and Pharmacy, University of Illinois. Pp. 142. New York: Commonwealth Fund, 1946. Price, \$1.50.

PREPARATION of this monograph was assigned to the author by the Committee on Medicine and the Changing Order of the New York Academy of Medicine. It is a discussion of medical education in America, and especially of the changes to be desired in the light of contemporary social progress. The author advocates a pre-medical education which offers opportunities for adequate preparation in the biologic and physical sciences, but avoids the dangers of too great concentration in pure science in order to allow sufficient time for studies in social science and the humanities. In the Medical School, he advocates lifting medical education above the level of mere training in the technology of medical practice. He desires more and better training in logical thinking, and in deductive and inductive reasoning. He would increase the emphasis given to the relation between the practice of medicine

and community needs. He seeks to make the internship an experience in the practice of preventive as well as of curative medicine, and to include in it family medicine as well as hospital and out-patient department medicine. He would organize residency and fellowship programs to place the responsibility for the student's progress and achievement squarely on the student himself. He is an advocate of increasing the programs of postgraduate teaching in the light of experience with the courses for returning veterans.

The program envisioned is an attractive one. It is not, of course, original with the author, but seems an able statement of the present trends in American medical education. Let us hope his wishes can be realized. I. S.

ENVIRONMENTAL WARMTH AND ITS MEASUREMENT. A Book of Reference Prepared for the Royal Naval Personnel Research Committee of the Medical Research Council. By T. BEDFORD, D.Sc., Ph.D., M.I.-MIN.E., Habitability Sub-Committee, the Royal Naval Personnel Research Committee. With a Preface by SURGEON VICE-ADMIRAL SIR SHELDON DUDLEY, K.C.B., O.B.E., M.D., F.R.C.P., F.R.S., K.H.P. Pp. 40; 10 ills. London: His Majesty's Stationery Office, 1946. Price, 70 cents.

THIS war manual was prepared for the information of Ships' Surgeons of the Royal Navy, but should be of interest to the specialist in the field. Citation of chapter headings suffices to indicate the ground covered: body-heat production and heat-loss; instrumental measurements; effective temperature and corrected effective temperature; procedure in making tests; ventilation reports; work at extreme temperatures. W. S.

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

MAY, 1947

ORIGINAL ARTICLES

STUDIES IN THE ORAL ADMINISTRATION OF PENICILLIN

I. ASSAYS OF VARIOUS PREPARATIONS AND THE DETERMINATION OF THE EFFECTIVE THERAPEUTIC DOSE*

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ASSAY OF ORAL PENICILLIN. It is now well established that the oral administration of penicillin can produce therapeutic plasma penicillin levels in spite of the fact that a portion of the penicillin is destroyed when in contact with gastric acid. Even before the Committee on Chemotherapeutic and Other Agents of the National Research Council had sanctioned the oral use of penicillin,^{7,11} a number of clinical reports of the therapeutic value of this dosage form had appeared.^{3,4,10} Gonorrhea and pneumococcal pneumonia have been shown to respond as readily to penicillin given orally as to that parenterally injected, and isolated examples of infection by other organisms sensitive to penicillin have been reported successfully treated by this procedure.

However, there are some poorly understood features of the problem of penicillin medication by mouth. The general practitioner has been given the impression either by direct statement or by implication that oral penicillin is worth while chiefly as an adjuvant for parenteral penicillin after the temperature has subsided

or for mild cases of infection and that it should not be used for any severe infection. He has also been led to believe that if penicillin by mouth is used under such circumscribed conditions the determination of the most effective dosage is not too important and that there need not be any concern over plasma penicillin levels or over the relation of the latter to penicillin sensitivity of the bacterium involved.

One important basis for this confused therapeutic reasoning has been that penicillin is inordinately expensive and that the quantities available for general distribution are limited and likely to remain so. Thus, although penicillin is no more harmful in large doses than in smaller ones, the therapeutic approach has been paradoxically to determine not the optimal but the minimal effective dose. Obviously, if price or limitations of supply were not involved, such an attitude would be recognized as therapeutically unsound. The consequences of such a point of view have been to tend to discredit oral penicillin and to reduce it almost to the category of a tonic.

* Aided by a grant from the Commercial Solvents Corporation, Terre Haute, Indiana.
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The present investigation, begun before oral penicillin was made generally available, was undertaken with the purpose of determining, if possible, the ultimate potentialities and the limitations of this therapeutic method. The hope was to achieve in oral penicillin a dosage form as adequate and as effective as that of parenterally injected penicillin, without the annoyance and pain and technical limitations of the latter. The present report deals with the assay of a number of oral preparations in order to determine an effective dosage. In the succeeding papers reports are made of the therapeutic results based on this dosage.

Method. Estimations of plasma penicillin concentration were made by *B. subtilis* serial dilution method of Randall, Price and Welch⁴ as modified by Hickey.⁵ In this modification, the multiple pipettings were made with a sterile pipetting machine and the inoculum used was a nutrient broth dilution (1.5 cc. to 100 cc.) of an 18 hour nutrient broth culture of *B. subtilis* (NNRL-B-558). The latter were prepared daily from stock agar slants by incubation on a shaking machine at 30° C. Serial dilutions of a standard penicillin solution (1 unit per cc. in a phosphate buffer at pH 6) usually produced 6 tubes with no growth. Thus an unknown serum similarly diluted and also producing 6 clear tubes would contain 1 unit per cc. The lower limit of penicillin concentration that could be estimated with such a standard was 0.031 unit per cc. Occasionally the standard showed 7 clear tubes which allowed measurements to 0.016 unit per cc. To insure greater accuracy of measurement 3 standard series were prepared for each day of assays. The results were discarded if the standards did not give consistent measurements. Blood was drawn for penicillin levels under aseptic conditions and transferred to tubes containing 0.02 gm. sodium citrate. The plasma was separated and used for the analyses. Serum was found to give the same values but its separation under sterile conditions proved inconvenient.

It has been alleged that *B. subtilis* has doubtful value as an organism for estimation of plasma penicillin level because

many blood specimens contain inhibitors of this bacterium even when penicillin is not present.^{1,2} To test this statement, control blood samples were taken for penicillin estimation before penicillin was administered in 40 assays. In addition, blood specimens from 80 hospital patients not on penicillin or sulfonamide therapy were analyzed for penicillin. In the total of 120 plasma specimens, only 1 showed a level equivalent to 0.03 unit; the rest gave zero levels. These findings, supplemented by the many zero levels in the hundreds of assays made during the studies, have convinced us that at least with our use of the method and possibly because of the employment of citrated plasma, there is little danger of finding positive penicillin levels in plasma specimens that do not contain penicillin.

The subjects used for assay of the various oral preparations of penicillin were so-called hospital controls, that is, those patients who were not acutely ill and who were believed not to have any circulatory or renal disturbances. They were, for the most part, young or middle-aged persons recuperating from herniorrhaphy or convalescing from some acute illness such as fracture, burn, or traumatic wound. After preliminary experiments had confirmed the now well-established fact that plasma penicillin levels were lower when penicillin was given after a meal than on an empty stomach, the routine established for assays was to give single doses of penicillin at 9 A.M., some 2 hours after breakfast. Blood samples were drawn at varying intervals after the dose without regard to the noon meal. When a priming dose was to be given first, this was administered at 8 A.M., and the second dose at 9 A.M., the time being counted from the second dose.

The oral preparations utilized in these studies were with 1 exception, especially prepared for us. Control studies were made with capsules containing crude calcium penicillin of about 700 units per mg. potency. These were put up in hard gelatin capsules and contained no buffer or

other diluent. These were called Capsules C. They were of several sizes: 25,000, 33,000 and 100,000 units per capsule. Capsules R.B. contained 25,000 units of the same crude calcium penicillin buffered with pectin hydrolysate. Capsules No. 10 contained 100,000 units of crystalline potassium penicillin, each containing 100,000 units. A variety of tablets were studied, most of which contained as the chief protecting agent a high melting fat. Some of these were discarded after only a few experiments. The tablets containing citrate were a marketed preparation. A brief description of those capsules and tablets on which extensive assays have been made is given in Table 1.

ce. However, they, as well as all other investigators in this field, are aware of the fact that many so-called sensitive organisms are not inhibited except by much higher concentrations than 0.03 unit per cc. Under any circumstance it is dangerous to translate directly such *in vitro* findings to *in vivo* conditions. Plasma penicillin levels should certainly be at least as high as that required for *in vitro* inhibition. They should probably be much higher if only to give assurance that all body fluids likely to contain the invading organism continuously have an effective penicillin concentration. Such an idea receives confirmation from the now well-established empirical finding

TABLE 1.—DESCRIPTION OF PENICILLIN CAPSULES AND TABLETS INVESTIGATED

Name	Type of penicillin	Diluent or buffer	Units per capsule or tablet
Capsules C	Crude calcium, 700 units per mg.	None	25,000; 33,000; 100,000
Capsules R. B.	Crude calcium, 700 units per mg.	Pectin hydrolysate	25,000
Capsules No. 10	Crystalline potassium, 1510 units per mg.	None	100,000
Capsules No. 11	Crystalline ammonium, 1500 units per mg.	None	100,000
Capsules No. 23	Crystalline potassium	Basic alum. acetate	25,000
Tablets No. 18	Crystalline potassium	Hydrogenated fat; soaps; starch	50,000; 100,000
Tablets No. 24	Crystalline potassium	Hydrogenated fat; soaps; mg. stearate	100,000
Tablets No. 35	Crystalline potassium	Sodium benzoate	50,000
Tablets No. 38	Crystalline potassium	Sodium sulfanilate	50,000

ASSAYS OF VARIOUS ORAL PREPARATIONS. *Criteria for Effective Plasma Penicillin Levels.* There has been no agreement as to what plasma penicillin concentration should be achieved to assure therapeutic effectiveness. The difficulty in estimating this concentration arises on the one hand from the variability in sensitivity to penicillin of the different organisms and the various strains of the same organism, and on the other hand from the rapidly changing plasma penicillin levels produced by the administration of penicillin. Findland and his colleagues⁸ have shown that most organisms sensitive to penicillin, especially gonococci and pneumococci, are inhibited in concentrations of less than 0.03 unit per

that doses of 20,000 units of penicillin intramuscularly every 3 hours are effective in most acute infections responsive to penicillin. Such injections have been found by us⁶ to give plasma levels, as determined by the *B. subtilis* method of assay, of 0.5 unit per cc. at $\frac{1}{2}$ hour, 0.06 at $2\frac{1}{2}$ hours and 0.03 at 3 hours. It appears from these considerations that the desirable plasma penicillin levels should be at least 0.03 unit per cc. at any time and higher than 0.06 most of the time. These criteria have been used as a guide in the determination of the required dosage of oral penicillin.

Dosage of 25,000 Units. Plasma penicillin levels determined after single or even repeated doses of 25,000 units proved dis-

appointing. Rarely were levels encountered higher than 0.03 unit per cc. Most frequently no perceptible levels were obtained. There were so many zero levels and there was so little difference between the various preparations, that it was useless to tabulate the results.

the least being obtained with the tablets buffered with sodium citrate. The levels in the third interval tended to be higher, but for the most part they ranged between 0.03 and 0.06 unit per cc., with an occasional 0.125 and a rare 0.25 unit per cc. The citrated tablets gave a higher average.

TABLE 2.—FREQUENCY DISTRIBUTION OF PLASMA PENICILLIN LEVELS AFTER FIRST AND THIRD DOSE OF 50,000 UNITS OF PENICILLIN GIVEN ORALLY EVERY 2 HOURS FOR 3 DOSES

Type of medication	Interval	Hour	Plasma penicillin concentration (units per cc.)					Arithmetical mean
			0 (<0.03)	0.031	0.062	0.125	0.25	
Capsules C	First	$\frac{1}{2}$	10	3	1	0.011
		2	9	3	2	0.015
	Third	$\frac{1}{2}$	6	4	3	1	..	0.028
Capsules R.B.	First	2	6	7	1	0.019
		$\frac{1}{2}$	9	3	1	0.012
	Third	2	8	5	0.012
Capsules No. 23	First	$\frac{1}{2}$	4	8	1	0.024
		2	6	6	1	0.019
	Third	$\frac{1}{2}$	5	4	3	0.025
Crystalline potassium penicillin in water	First	2	7	3	2	0.016
		$\frac{1}{2}$	2	6	3	1	..	0.038
	Third	2	3	6	3	0.030
Tablets No. 18	First	$\frac{1}{2}$	8	2	2	0.015
		2	5	6	1	0.020
	Third	$\frac{1}{2}$..	5	5	2	..	0.053
Tablets No. 35	First	2	2	8	1	1	..	0.033
		$\frac{1}{2}$	7	6	1	0.017
	Third	2	5	6	3	0.026
Tablets No. 38	First	$\frac{1}{2}$	2	7	4	1	..	0.039
		2	1	7	4	2	..	0.047
	Third	$\frac{1}{2}$	3	7	1	1	..	0.030
Tablet with sodium citrate (commercial)	First	2	6	4	..	2	..	0.025
		$\frac{1}{2}$	1	6	4	0.045
	Third	2	1	6	4	1	..	0.043
Tablet with sodium citrate (commercial)	First	$\frac{1}{2}$	9	3	5	2	1	0.045
		2	9	8	3	0.022
	Third	$\frac{1}{2}$	3	6	9	2	..	0.050
Tablet with sodium citrate (commercial)	First	2	7	8	3	2	..	0.034
		$\frac{1}{2}$	2	6	3	1	..	0.038
	Third	2	1	2	7	2	..	0.055
Tablet with sodium citrate (commercial)	First	$\frac{1}{2}$	1	2	6	3	..	0.058
		2	1	3	6	2	..	0.053

Dosage of 50,000 Units. On the possibility that 50,000 units of penicillin every 2 hours might be a satisfactory oral dosage of penicillin, 8 different preparations were assayed as follows: 50,000 units were given to hospital control subjects every 2 hours for 3 doses, and blood was drawn at $\frac{1}{2}$ and 2 hours after the first and after the third dose. A total of 109 assays involving 436 plasma penicillin level determinations were carried out. The results are summarized in Table 2. There were a large number of zero levels, particularly in the first interval for all the preparations,

chiefly because they produced fewer zero levels. In general the data indicated that while it was possible to attain therapeutic penicillin levels with doses of 50,000 units given every 2 hours, there were still too many zero levels and too few 0.125 or higher levels to make this dosage as reliable for use in severe infections as that of 20,000 units parenterally every 3 hours. The data also indicated that, with the exception of the lowered tendency to zero levels shown by the citrated preparations, there was no great difference in the various preparations.

That the prevailing plasma levels were higher in the third interval than in the first was undoubtedly due to the "priming" effect of the first 2 doses. Penicillin with the first doses was distributed to all the body fluids leaving a residual concentration at the end of each interval which, though not necessarily high enough to be measurable, allowed the attainment of a higher level with the succeeding doses. In the parenteral administration of penicillin there is little use for this priming effect, for the plasma levels immediately after the injection are so high as to be little affected by residual penicillin concentrations from the previous dose. But with orally administered penicillin where the absorption is slow and where the early plasma concentrations are not so great

units at 9 A.M., blood being drawn at intervals after the 9 A.M. dose. The plasma levels obtained were found to be of the same order as those in the therapeutic studies to be reported.

Table 3 shows the frequency distribution of plasma penicillin levels with one of the preparations studied, crystalline potassium penicillin in gelatin capsules (Capsules No. 10). The levels were determined for $\frac{1}{2}$ hour periods after the 9 A.M. dose of 100,000 units, but in any single assay no more than 4 determinations were carried out. However, by the use of a large number of assays with penicillin determinations made at varying intervals, it was possible to cover each $\frac{1}{2}$ hour period up to $5\frac{1}{2}$ hours. From Table 3 it can be seen that there was a marked variability

TABLE 3.—DISTRIBUTION OF PLASMA PENICILLIN LEVELS AFTER ADMINISTRATION OF PENICILLIN CAPSULES NO. 10 IN A DOSE OF 200,000 UNITS FOLLOWED IN 1 HOUR BY 100,000 UNITS IN 52 SUBJECTS

Weighted value	Units (per cc.)	Hours after administration of 100,000 units											
		$\frac{1}{2}$	1	$1\frac{1}{2}$	2	$2\frac{1}{2}$	3	$3\frac{1}{2}$	4	$4\frac{1}{2}$	5	$5\frac{1}{2}$	
6	0.5	1	3	1	
5	0.25	4	4	4	4	..	4	
4	0.125	7	6	4	2	3	4	..	2	3	
3	0.062	..	1	3	3	4	3	3	4	2	2	1	
2	0.03	2	2	1	4	4	8	6	2	4	5	..	
1	0	1	3	3	9	8	12	12	
Average	..	0.174	0.211	0.143	0.120	0.063	0.106	0.031	0.034	0.037	0.020	0.005	
Mode	..	0.125	0.125	0.125	?	0.06	0.03	0.03	0.0	0.0	0.03	0	
Median	..	0.125	0.125	0.125	0.06	0.06	0.06	0.03	0.03	0.03	0.03	..	
Weighted average	..	0.138	0.163	0.122	0.087	0.056	0.057	0.04	0.03	0.03	0.018	0.012	

as those obtained with parenteral injections, the priming effect of the previous doses becomes an important factor in helping achieve therapeutic concentrations, as in the oral administration of sulfa compounds. This finding was made use of in the establishment of the therapeutic regimens.

Dosage of 100,000 Units. Preliminary experiments with oral doses of 100,000 units of penicillin demonstrated that a satisfactory range of plasma levels could be achieved. For the purpose of simulating in single assays the conditions obtaining when doses of 100,000 units were used in actual therapy after a larger priming dose of 200,000 units, a series of comparative assays of the various oral preparations was made in which 200,000 units were administered at 8 A.M., followed by 100,000

in the plasma levels at any period, much greater than that found after parenteral injections of penicillin. Several types of averages were determined for each period: mode, median, arithmetical mean and "weighted average." The last, a form of the geometric mean, was obtained by giving a linear weighting—1 for values less than 0.03, 2 for 0.03, etc.—for each of the geometrically progressing plasma penicillin levels, determining the arithmetical mean of these values, and transposing back into units per cc. The conclusions that can be drawn from the data are the same whichever form of average is utilized, but since the weighted average appears to give the smoothest curves, it has been used in the comparisons of the various preparations.

During the 1st hour, the range of pen-

icillin levels after the administration of capsules of potassium penicillin was from 0.5 to 0.03 unit per cc. The modal and median values were 0.125 unit per cc. and the arithmetical and geometrical mean were both between 0.125 and 0.25 unit per cc. The peak mean value appeared in this series to be at 1 hour, but it might be that the difference between the values at 1 hour and those at $\frac{1}{2}$ hour was not significant. There were no zero values during the first 2 hours. At 3 hours a considerable number of zero units per cc. concentrations began to appear, and at 4 hours it became the prevailing concentration. Yet, even at 5 hours, 7 out of 19 determinations were 0.03 unit per cc. or higher. The averages obtained over the 5 hour period indicate that though

ected with a high melting fat. However, several types of tablets, 1 of which, Tablet No. 24, is shown in Table 4, apparently disintegrated too slowly to give as high levels as the other preparations. A slight distinction between the various preparations seemed to be present at the $4\frac{1}{2}$ and 5 hour period. At this stage only Capsules No. 10, Tablets No. 18 and probably penicillin tablets containing citrate appeared to produce any significant plasma penicillin levels, usually 0.03 unit per cc. On the whole, the data imply that almost any form of penicillin, if given in doses of 100,000 units after a priming dose, will produce good plasma levels persisting in the therapeutic range for 3 or more hours. If this dose were used every 3 hours, a residual plasma (and body fluid) concen-

TABLE 4.—COMPARISON OF AVERAGE VALUES FOR PLASMA PENICILLIN LEVELS AFTER ADMINISTRATION OF 200,000 UNITS FOLLOWED IN 1 HOUR BY 100,000 UNITS FOR VARIOUS TYPES OF CAPSULES AND TABLETS

No subjects	Preparation	Hours after administration of 100,000 units											
		$\frac{1}{2}$	1	$1\frac{1}{2}$	2	$2\frac{1}{2}$	3	$3\frac{1}{2}$	4	$4\frac{1}{2}$	5	$5\frac{1}{2}$	
49	Tablets No 18	0 150	0 163	0 119	0 119	0 059	0 062	0 044	0 034	0 034	0 025	0	
52	Capsules No 10	0 138	0 163	0 119	0 088	0 056	0 059	0 039	0 031	0 031	0 18	0 012	
29	Capsules No 11	0 213	0 106	0 110	0 073	0 056	0 046	0 046	0 031	0 016	0 006	0	
19	Tablets No 24	0 031	0 062		0 034		0 034		0 016		0 016		
35	Capsules R B	0 275	0 125	0 150	0 125		0 100		0 039	0 016	0 012	0	
35	Capsules A control	0 163	0 138	0 110	0 073		0 049	0 028	0 034	0 003	0 006	0	
25	Tablets with sodium citrate (commercial)		0 210		0 119				0 043			0 007	

the initial levels were not usually as high as those obtained with single parenteral injections of 20,000 units, nevertheless good therapeutic levels were maintained for at least 3 and possibly for 4 hours.

A comparison of 8 different preparations in assays made after a priming dose of 200,000 units followed in 1 hour with a dose of 100,000 units as shown in Table 4. The weighted average as determined above was used as the basis for comparison. The most striking feature of these data was that there was on the whole very little difference in the levels achieved, no matter what preparation was used. Crude penicillin alone in capsules produced almost the same values as did crude penicillin protected with pectin. Pure potassium penicillin gave levels not greatly different from potassium penicillin pro-

tection would tend progressively to raise the plasma level with each dose.

Larger Doses. In isolated experiments, single doses from 200,000 to 360,000 units of varying preparations have been used for assays, blood specimens being taken up to 6 hours after the dose. In most of these the levels achieved in the 1st hours were not greatly different from those for 100,000 with a 200,000 unit priming dose. However, there was a greater tendency for prolongation of penicillin levels to 6 hours. In another group of experiments, Tablets No. 18 were given in doses of 200,000 units every 8 hours for 3 doses and blood levels taken after the last dose. The results are shown in Table 5. It can be seen that the levels were not much higher in the 1st hour than those found after administration of a priming dose of 200,000 units

followed in 1 hour by 100,000 units. However, the significant finding was that appreciable levels were usually present at 6 hours after the last dose and not infrequently after 8 hours. These results would seem to indicate that there would be little harm in giving a double dosage before bedtime and allowing the patient to go through the night without being awakened for further penicillin medication.

achieved, but there were too many zero levels and too few levels higher than 0.06 unit per cc. to make the dosage a reliable substitute for parenteral therapy.

Doses of 100,000 units, when preceded by a primary dose of 200,000 units 1 hour earlier, gave levels averaging higher than 0.125 unit per cc. for the first 2 hours and about 0.06 unit for the next 2 hours. Such levels were comparable with those

TABLE 5.—PLASMA PENICILLIN LEVELS AFTER ADMINISTRATION OF TABLETS NO. 18 IN DOSES OF 200,000 UNITS EVERY 8 HOURS FOR 3 DOSES

Subject	Hours after third dose (units per cc.)							
	1	2	3	4	5	6	7	8
Se.	..	0.25	..	0.125	..	0.125	..	0.06
Ba.	..	0.25	..	0.125	..	0.125	..	0
Mcl.	..	0.5	..	0.25	..	0.125	..	0.03
Hi.	..	0.5	0.25	..	0.06
Hi.	..	0.25	..	0.06	..	0.06	..	0
Ro.	..	0.03	0.06	..	0.03
Jo.	0.06	..	0.06	0.125	..	0.06
Be.	0.03	0.03	..	0.03
Re.	0.25	0.06	..	0
Fr.	..	0.125	0.03	..	0
Co.	..	0.25	0.06	..	0.03
Ka.	..	0.06	0.03	..	0

Summary and Conclusions. Assays of the plasma penicillin levels achievable with varying doses of penicillin orally administered were made with a large variety of preparations, with and without diluents, anti-acid substances, or buffers.

Doses of 25,000 units were ineffective usually in producing appreciable plasma penicillin levels. When 50,000 units were administered every 2 hours, plasma levels of 0.06 unit per cc. were frequently

obtained with intramuscular injections of 20,000 units every 3 hours. At this dosage there were no great differences in the results with the various preparations.

Doses of 200,000 units gave perceptible plasma levels even at 6 and 8 hours after the dose.

From these findings, the therapeutic regimen established was a primary dose of 200,000 units followed by 100,000 units every 3 hours.

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STUDIES IN THE ORAL ADMINISTRATION OF PENICILLIN

II. RESULTS OF TREATMENT OF PNEUMOCOCCIC LOBAR PNEUMONIA AND OTHER ACUTE INFECTIONS WITH SEVERAL ORAL PENICILLIN PREPARATIONS*

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ORAL PENICILLIN THERAPY. In a series of assays of capsules and tablets of penicillin designed for oral use, it has been shown² that doses of 100,000 units every 3 hours, preceded by a primary dose of 200,000 units, would give therapeutically effective plasma penicillin levels, comparable with those obtained with 20,000 units intramuscularly every 3 hours. With this basis for therapy, a series of patients with bacterial infections known to be responsive to penicillin were treated by oral administration of several of the preparations assayed. This paper is a report of the results of such treatment.

The patients studied could be divided into 2 groups: those having pneumococcic lobar pneumonia and those having a miscellaneous group of infections other than pneumonia. In all cases an attempt was made to determine the causative organism, to obtain confirmation of the diagnosis by Roentgen ray if possible, to get white cell counts and temperature curves, and to determine representative plasma penicillin levels. However, in a large group of cases, no such control could be obtained. Since in these cases only a clinical evaluation could be used to measure the success of the treatment, they have not been included in the tabulation of results. They are, however, included in the evaluation of toxic reactions.

The regimen established was as follows: As soon as the clinical diagnosis was made, a dose of 200,000 units of penicillin was administered orally. Then, 100,000 units were given orally every 3 hours on a 3, 6, 9 and 12 o'clock schedule. This schedule

avoided all meals, except the noon meal, since these were given at 7, 11:30, 4:30 and 8 o'clock (evening nourishment). No other effort was made to rule out the effect of food on the absorption of penicillin. The medication was continued for at least 3 days or usually at least 48 hours after the temperature had returned to normal. The usual sustaining medication was allowed, especially codein sulfate for cough; but aspirin was not permitted because of its possible antipyretic effect. Parenteral fluids and oxygen were administered if necessary.

Pneumococcic Lobar Pneumonia. Since the purpose of these therapeutic studies was to determine merely whether orally administered penicillin could accomplish everything that parenterally injected penicillin has been known to do, the patients chosen for the most part were manifest cases of uncomplicated pneumonia. However, since the decision for the initial treatment was in the hands of the interne (the majority of patients with pneumonia being admitted during the night) many doubtful cases were chosen. Where later clinical examination, laboratory finding and Roentgen ray evidence indicated a mistake in the diagnosis, the cases were discarded from the study. In quite a few cases, on the other hand, though clinical and Roentgen ray evidence indicated the presence of lobar pneumonia, the bacterial examination of the sputum (including passage through a mouse) and of the blood, and the white count, left the impression of an atypical virus pneumonia. These cases have, nevertheless, been included

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TABLE 1.—THE EFFECT OF PENICILLIN CAPSULES R.B. ON THE TREATMENT OF PNEUMOCOCCIC LOBAR PNEUMONIA
Dosage: 200,000 Units Initially, Followed by 100,000 Units Every 3 Hours

Plasma penicillin levels in random specimens on successive days of treatment													
Case	Age	Days of illness before penicillin treatment	Initial W.B.C. count	Lobe location as shown by Roentgen ray	Maximal temperature (° F.)	Hours for temperature to fall to normal	Total hours of treatment	Hours after previous dose of penicillin (units per cc.)					Remarks
								1	1½	2	2½	3	
			17,500	R.U.L.	103.6	12	124	0.125	..	0.06	100,000 units every 4 hours after 1st day
2	40		25,900	R.L.L.	102.2	20	84	0.03	..	0.125	..	0.06	
								0.5	0.06	0.125	
								0.03	0.06	
								0.125	..	0.03	
3	36	1	14,000	R.L.L.	103.6	12	56	0.03	..	0.03	Pneumococcus found by mouse inocula- tion and bile test
4	38	5	9,750	L.L.L.	102.6	12	61	0.125	..	0.06	
								0.06	
								0.125	..	0.03	
								0.125	..	0.25	..	0.25	
6	33	4	12,350	L.L.L.	102.8	30	75	0.03	..	0.06	Pneumococcus found by mouse inocula- tion and bile test Type XIX pneumo- coccus found by ino- culation of mouse and bile test
								0.03	..	0.03	
								0.03	..	0.06	
								0.06	..	0.25	
								0.125	..	0.25	..	0.03	
7	39	2	13,700	L.L.L.	104.0	20	82	0.06	..	0.06	Pneumococcus found by mouse inocula- tion and bile test Type XIX pneumo- coccus found by ino- culation of mouse and bile test
								0.03	..	0.25	
								0.03	..	0.125	
								0.25	0.125	0.25	
								0.06	..	0.06	
8	54	2	21,100	R.L.	101.0	20	97	0.25	..	0.25	Pneumococcus found by mouse inocula- tion and bile test
								0.03	..	0.06	
								0.06	..	0.25	
								0.25	0.125	0.25	
								0.06	..	0.06	
9	28	2	16,100	R.L.L.	101.4	80	156	..	0.03	0	..	0.06	Pneumococcus found by mouse inocula- tion and bile test
								0.03	
								0.03	..	0	..	0.06	
								0.03	
								0.03	..	0.06	
10	14	3	20,500	R.U.L.	104.2	12	106	0.03	..	0	..	0.03	Pneumococcus found by mouse inocula- tion and bile test
								0.06	
								0.03	..	0.03	Pneumococcus found by mouse inocula- tion and bile test
								0.03	..	0.06	

and, as will be seen, often showed equivocal results. The type of pneumococcus and the presence of bacteremia were not routinely determined in this series, for it was not primarily a study of pneumonia. However, in another investigation to be reported typing was carried out routinely and a correlation attempted of the type of pneumococcus with the results of penicillin treatment.

normal levels within 12 hours in 4 cases, within 20 hours in 7 cases and within 30 hours in 9 cases. Only 1 patient required treatment for more than 2 days before there was a fall to normal temperature. With the subsidence of the fever, there was also a corresponding restoration of normal pulse and respiratory rate, and this occurred in spite of the fact that the physical findings in the chest

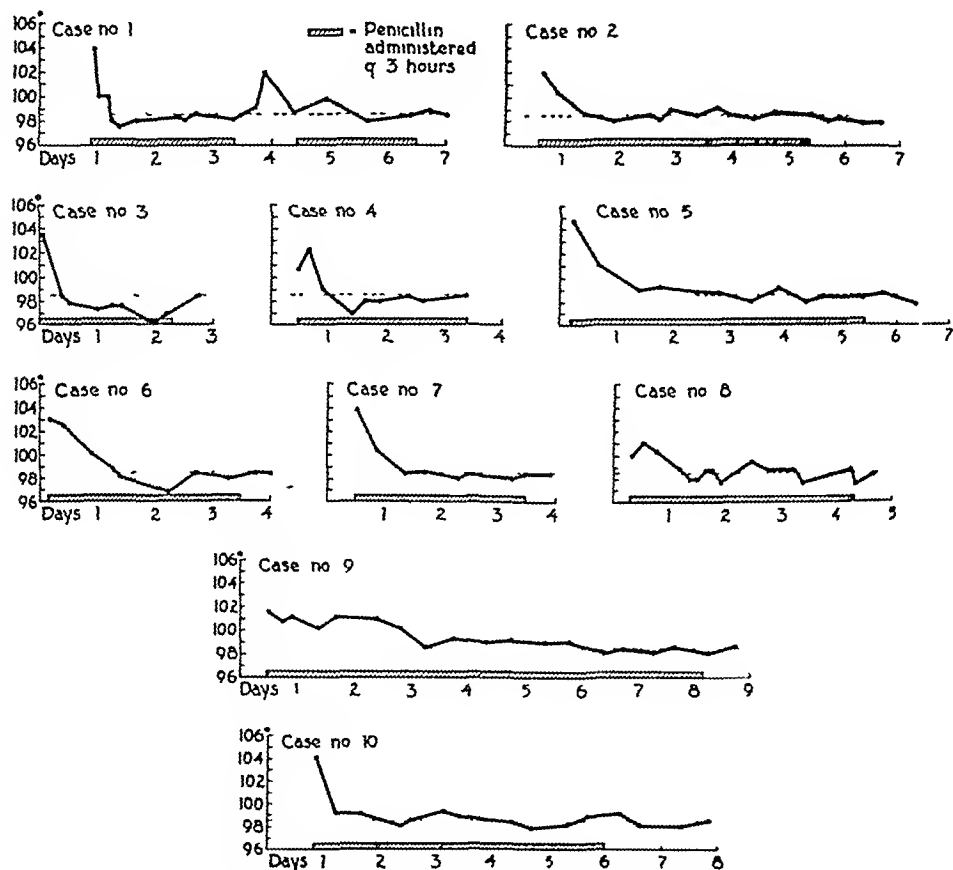


FIG 1 — Temperature curves in 10 cases of pneumococcal pneumonia treated with penicillin Capsules R.B. (with pectin hydrolysate).

Ten patients with lobar pneumonia were treated with Capsules R.B. (These contained pectin hydrolysate as a buffer. A description of the various preparations is given in Table 1 of the previous paper.) The pertinent data in these cases are shown in Table 1 and the temperature curve in Figure 1. It can be seen that the temperature dropped to approximately

were apparently unchanged. In other words, though consolidation of the lungs was still present, the toxic symptoms had disappeared. This finding was confirmed by Roentgen ray at this state.

In several cases in this group, as in the succeeding groups, there was a secondary rise in temperature, usually on the 3rd or 4th day of penicillin treatment. The

rise was usually small (1 or 2 degrees) and was difficult to explain, since the patients were getting penicillin regularly and were showing plasma levels of 0.03 unit per cc. or higher even at 3 hours after the dose. In Case 1, the temperature rise occurred during the period of 24 hours when penicillin was omitted by mistake; the rise in this case might mean a recrudescence of the pneumococcal disease, but, in other cases, there was no such explanation possible. This secondary rise has been found to occur even in the treatment of pneumonia with parenteral penicillin.³ The secondary rise might be explained in either 1 or 2 ways: (1) it represented a residual virus infection present along with the pneumococcal infection, or (2) it was associated with the absorption of toxic split products from the resolving consolidation in the alveoli. Whatever the explanation, such small elevations were not unlike those seen at times following the natural immunologic crisis of lobar pneumonia.

The poorest clinical results were obtained in Case 9. The temperature did not fall to the neighborhood of normal for 80 hours and even then there was a further rise during the next 16 hours. Thereafter, the patient improved rapidly, Roentgen rays taken 7 days after the initial ones showed complete resolution of the pneumonic process. The reason for the slow results in this case may be found in the plasma penicillin levels achieved. In 4 of the 6 assays, there was no measurable amount of penicillin in the blood. The plasma level was probably too low for optimal bacteriostasis. In such a case it would probably have been wise to have increased the dosage at the end of the 2nd day.

Twenty patients with lobar pneumonia were treated with Capsules No. 10 (crystalline potassium penicillin). A summary of the pertinent data is shown in Table 2 and the temperature curves are shown graphically in Figure 2, A and B. Nine of the 20 patients experienced a drop to approximately normal temperature within

24 hours. - In 6 more cases, the temperature fell during the 2nd day of treatment. In the remaining 5 cases, the subsidence of the fever was slow and it was doubtful whether the penicillin did any good other than to prevent complications. In Case 53 pneumococci were never isolated and since the white count was low, the patient may have had a virus pneumonia. Case 58 was complicated by heart disease, and there was the suspicion of rheumatic fever as a further complication. It was possible that other cases showed complicating infections. In Case 64 a secondary rise in temperature occurred when penicillin was omitted by mistake for more than a day. There was a prompt fall of temperature upon renewal of penicillin medication. Yet in several other cases a secondary rise in temperature occurred even during penicillin medication as in the group treated with the penicillin buffered with pectin hydrolysate.

Another group of 10 patients with lobar pneumonia were given Tablets No. 18 (pure potassium penicillin in a high melting fat). The data in these cases are summarized in Table 3 and the temperature curves are shown in Figure 3. These patients developed pneumonia in the late winter or early spring and appeared to be much sicker than those of the previous groups who were treated in the fall. Yet 5 of these experienced a prompt subsidence of fever within 24 hours. Three others required 48 hours for the initial fall in temperature, and 2 patients required much longer treatment. In this group, the pneumococci were typed and blood cultures were made. Of the 7 cases that showed pneumococci in the sputum, 1 was of Type I, 3 of Type II, 1 of Type IV, 1 of Type VII and 1 of Type XVI. There was no determinable correlation between the type and the severity of the disease or the response to penicillin. On the other hand, all 5 cases which showed the response within 24 hours had negative blood cultures. There were 2 cases with positive cultures, 1 of Type I which required 48 hours for the return of the tem-

TABLE 2.—THE EFFECT OF PENICILLIN CAPSULES NO. 10 ON THE TREATMENT OF PNEUMOCOCCIC LOBAR PNEUMONIA
Plasma penicillin levels in random specimens on successive days of treatment (units per cc.)

Case	Age	Days of illness before penicillin treatment	Initial W.B.C. count	Lobe location as shown by Roentgen ray	Maximal temperature (° F.)	Hours for temperature to fall to normal	Total hours of treatment	Hours after previous dose of penicillin			
								1	1½	2	3
51	42	4	17,700	R.M.L.	101.8	12	58	0.06	
52	36	4	13,650	L.L.L.	101.0	91	160	0.25	..	0.125 0.06 0.06	
								0.25	0.25	0.03 0.06 0.125	
53*	41	15	6,550	R.L.L.	104.5	183	108	0.06 0.03	0.03
								0.03	0.03	0.03	..
								0.125	0.03
54	49	5	17,350	R.L.L.	103.2	20	81	0.03	..
								0.125	0.03
55	29	1	4,500	L.L.L.	101.8	36	144	0.125	..	0.03	..
								0.125	0.06
56	29	1	18,500	R.L.L.	102.0	20	128	0.125	..
57	31	5	18,000	R.L.L.	102.4	104	92	0.06	..
58	16	5	11,650	Heart disease L.L.L.	104.0	20	141	0.06	0.5
59	14	4	11,450	L.L.L.	103.2	30	61	0.06	0.06	0.03	..
								0.25	0.125
60	19	4	8,500	L.L.L.	101.0	20	126	0.125 0.125 0.5	0.125
								0.125	0.125
61	76	4	18,900	L.L.L.	101.0	12	102	0.03	0.03	0.125	0.125
62†	65	16	10,900	R.L.L.	101.2	30	206	0.125	0.125
63	25	2	36,000	R.L.L.	104.0	128		0.25	0.25	0.125 0.25	0.25
								0.125	0.25
64	19	4	35,000	R.L.L.				0.125	0.25

TABLE 3.—THE EFFECT OF PENICILLIN TABLETS NO. 18 ON THE TREATMENT OF PNEUMOCOCCIC LOBAR PNEUMONIA
Dosage: 200,000 Units Initially, Followed by 100,000 Units Every 3 Hours

Plasma penicillin levels in random specimens
 on successive days of treatment
 (units per cc.)

Case	Age	Days of illness before penicillin treatment	Initial W.B.C. count	Lobe location as shown by Roentgen ray	Maximal temperature (° F.)	Hours for temperature to fall to normal	Total hours of treatment	Hours after previous dose of penicillin				Remarks	
								1	1½	2	2½		3
81	36	1	50,000	R.L.L.	101.6	24	86	0.03	..	Type II
82	33	4	7,600	R.M.L.	105.0	24	72	0.25	0.03	..	Type XVI
83	32	3	15,500	L.L.L.	104.2	24	96	..	0.06	Type VII
84	21	1	12,600	R.L.L.	102.0	10	96	0.125	0.06	..	Type IV
85	42	3	8,600	L.L.L.	104.0	24	168	0.06	Type I; blood culture positive
86	40	2	14,600	L.L.L.	102.4	24	72	0.06	..	Type I; blood culture positive
87	40	1	7,500	R.L.L.	100.5	48	192	0.125	..	0.06	Type III
88	23	1	5,500	Lobes R.L.L.	103.5	192	264	Type III
89	33	7	20,400	R.M.L.	100.8	144	216	0.25	Type II; blood culture positive
90	62	4	30,200	L.L.L.	103.6	240	264	0.25	Type II; blood culture positive

* Pneumococcus not isolated.

† Treated previously unsuccessfully with sulfadiazine.

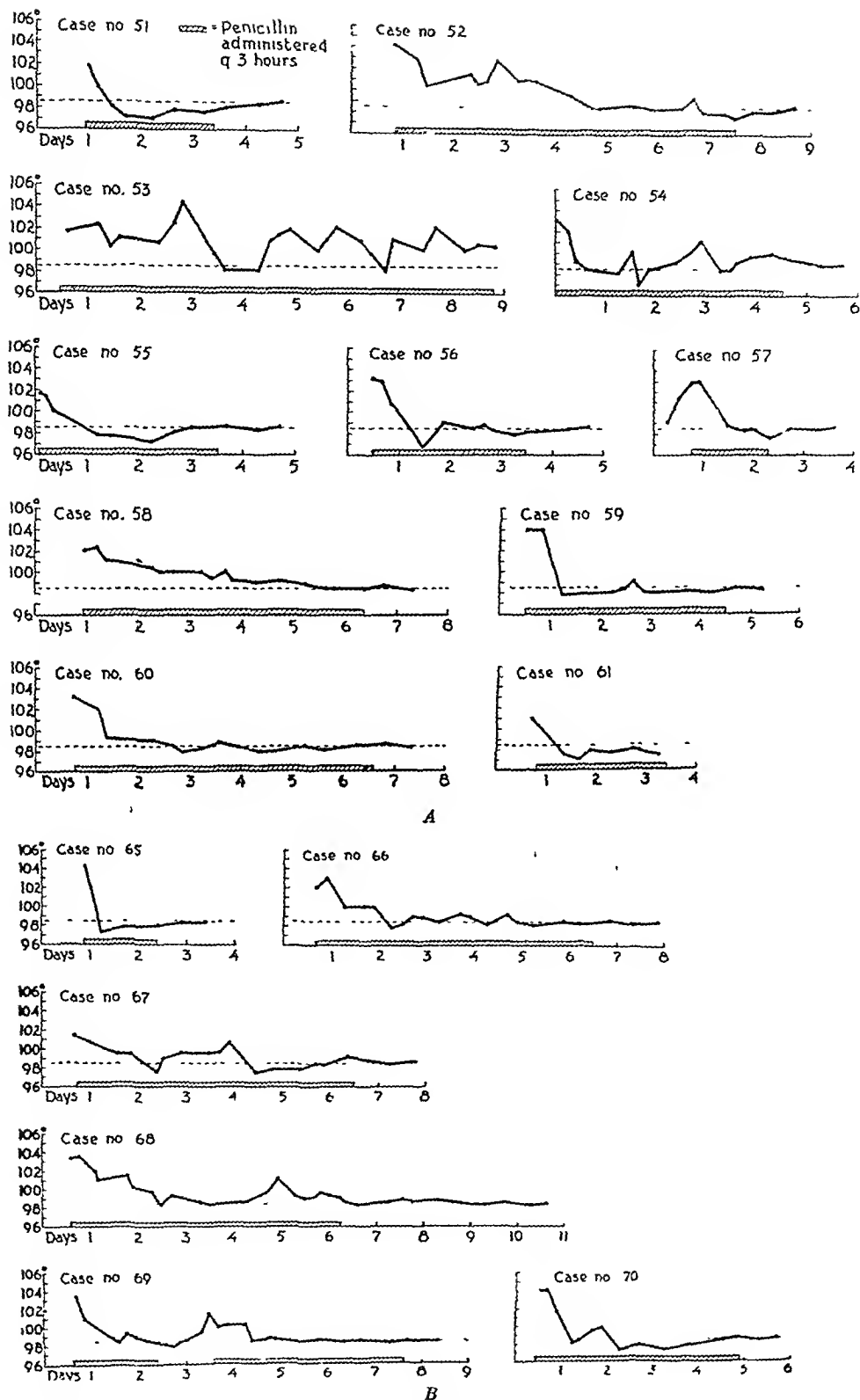


FIG. 2.—A and B. Temperature curves in 20 cases of pneumococcal pneumonia treated with Capsules No. 10 (crystalline potassium penicillin).

perature to normal, and 1 of Type II which had not responded until after 6 days of treatment. It is now well recognized that the patients showing bacteremia respond less effectively to chemotherapeutic agents.

Secondary rises in temperature occurred in several of these cases. In Case 88, the

daily "spiking" of the temperature after the initial fall was suspiciously like that of an abscess, though none could be discovered. Perhaps a non-specific bronchitis (as is so frequently found in such cases) produced by a bacterium resistant to penicillin was responsible for the secondary rise in this case.

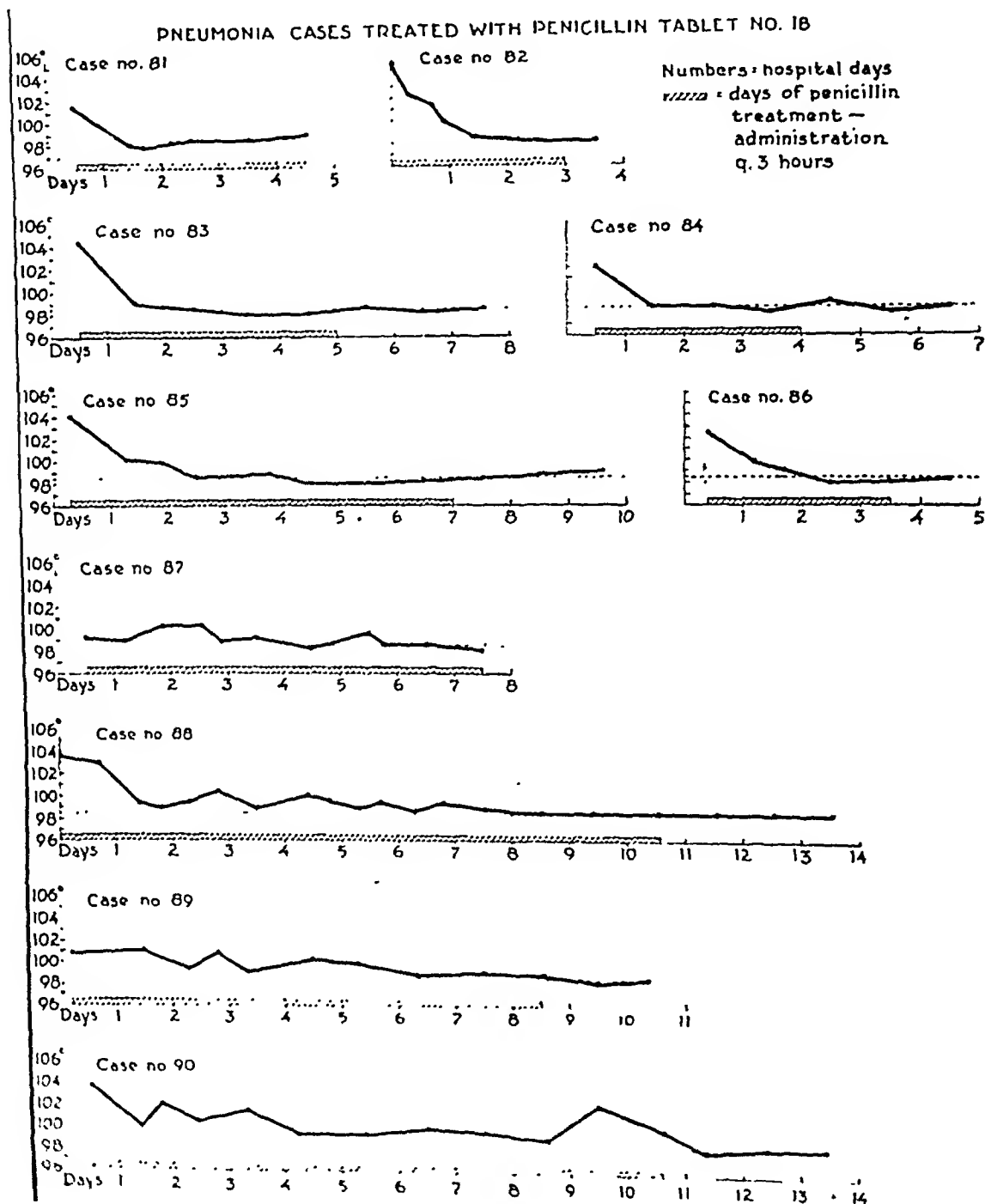


Fig. 3. -Temperature curves in 10 cases of pneumococcal pneumonia treated with Tablets No. 18 (potassium penicillin in a high melting fat).

TABLE 1.—THE EFFECT OF PENICILLIN CAPSULES C ON THE TREATMENT OF PNEUMOCOCCIC LOBAR PNEUMONIA
Plasma penicillin levels in random specimens
on successive days of treatment
(units per cc.)

Case	Age	Days of illness before penicillin treatment	Initial W.B.C. count	Lobe location as shown by Roentgen ray	Maximal temperature (°F.)	Hours for temperature to fall to normal	Total hours of treatment	Hours after previous dose of penicillin			Remarks
								1	2	3	
101	43	1	11,600	R.L.L.	101.2	30	140	..	0.25	..	Mouse inoculation neg. for pneumococcus
102	43	5	16,700	Bilat.	101.2	48	179	..	0.25	..	
103	34	4	4,950	R.L.L.	101.2	110	209	..	0.03	0.25	
104	36	5	19,550	R.L.L.	103.6	133	210	0.06	0.25	0.125	
105	32	1	7,900	R.L.L.	102.0	12	120	0.25	0.03	0.125	Type X
106	26	1	26,000	L.L.L.	104.6	30	120	0.25	0.03	0.125	Blood culture, positive Type II
107	17	2	11,700	L.L.L.	101.0	30	120	0.25	0.03	0.125	
108	42	5	11,200	R.L.L.	102.8	30	120	0.25	0.03	0.125	
109	40	7	23,900	L.L.L.	106.8	120	120	0.125	0.06	0.125	

Nine more patients were treated with the control Capsules C (crude calcium penicillin). The data for these cases are shown in Table 4 and the temperature curves in Figure 4. The 1 death in the whole series of 49 cases occurred in this group after 4 days of treatment. This patient had a bilateral pneumonia but,

Of the remaining 8 patients treated with the control capsules, 1 showed a critical fall in temperature within 12 hours, 3 more within 36 hours, 1 more in 48 hours and 3 required 5 to 6 days for a subsidence of the fever. In 1 of the 3 resistant cases (Case 109), the blood culture was known to be positive and Type II pneumococcus

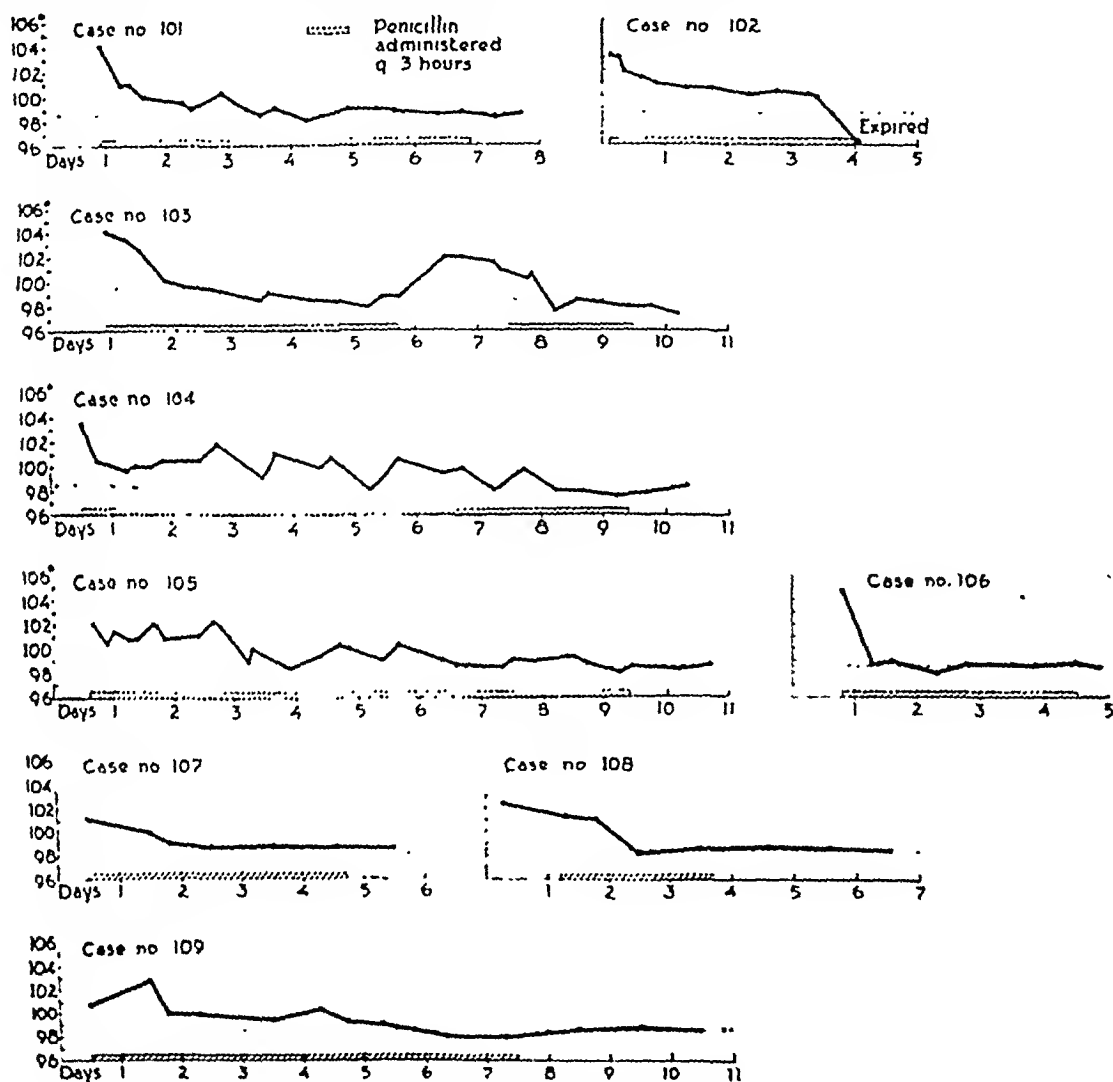


FIG. 4.—Temperature curves in 9 cases of pneumococcal pneumonia treated with Capsules C (crude calcium penicillin).

though the white count was 16,200, pneumococci were not isolated from the sputum or blood or from the peritoneum of a mouse inoculated with the sputum. The plasma penicillin levels were satisfactory; in fact, on the 3rd day 1 unit per cc. was achieved. This high level was probably related to the failing circulatory and renal efficiency of the patient.

was isolated. In Case 104 a pneumococcus was isolated by mouse inoculation. The failure in this case to achieve good results with penicillin was difficult to understand, for 4 of 6 plasma penicillin determinations showed levels of 0.25 unit per cc. or higher. On the other hand, in Case 105, the other unsuccessful case, the failure might have been due to poor absorption

of penicillin, for 3 out of 7 determinations showed imperceptible levels and 2 others showed no higher than 0.06 unit per cc. at 2 hours after a dose. Secondary rises in temperature occurred in this group as in the others. In Case 103, it occurred after penicillin had been stopped, and promptly subsided on resumption of penicillin therapy.

In comparison with the other groups, the capsules of crude unbuffered penicillin appeared to give the poorest clinical results. Yet, the number of cases studied were too few to allow a definite conclusion to be drawn, particularly since these cases were not selected from the same epidemic of pneumonia as those of any other group. *Those patients who responded to penicillin* did so as promptly as those on the other preparations. Also, there were no considerable differences between the blood levels obtained with Capsules C, both in the assays and in the pneumonia cases, and those obtained with the other preparations. These facts would tend to make the 1 death and the higher percentage of poor results in this small group a fortuitous finding. If it is true that these capsules are therapeutically inferior to the other preparations of the purer forms of penicillin, the reason for the inferiority is difficult to ascertain.

The plasma penicillin levels in the 4 groups of patients were taken at varying intervals after a dose of penicillin. Usually the 9 A.M. dose was chosen. The levels ranged from 1 to 0 units per cc. but the prevailing value at 1 and 2 hours was 0.125 and at 3 hours 0.06 unit per cc., quite as was found in the assays of 100,000 units dosage after a primary dose of 200,000 units. In some of the cases in which persistently low levels were found, the clinical results seemed to be correlated with these low levels. But this was not always so, for in several cases prompt remission of fever and toxicity occurred even with low plasma penicillin levels. This is, of course, in accordance with the recognized sensitivity of most pneumococci to penicillin. In the 3 cases in which

penicillin sensitivity was determined by the serial dilution method, growth of the pneumococci was inhibited in penicillin concentrations *in vitro* of 0.01 unit per cc.

Miscellaneous Infections. Table 5 gives a list of cases of miscellaneous acute infections treated with 3 of the oral preparations, namely, Capsules R.B., Capsules No. 10 and Tablets No. 18. Since it was desirable to obtain in these cases a definite bacteriologic diagnosis, the cases chosen were of necessity for the most part otolaryngologic or suppurative external lesions. The regimen was the same as in the cases of pneumonia, a primary dose of 200,000 units followed by 100,000 units every 3 hours. No perceptible difference in the clinical results could be noticed. In general, the results of the oral penicillin therapy in these cases was as good as those obtained with parenterally administered penicillin. The subsidence of fever usually occurred in 12 to 36 hours, especially when the offending organism was a *Strep. hemolyticus*. The staphylococcal infections were more resistant, as was to be expected, but the clinical response to penicillin management in these cases was easily recognizable as superior to that with purely expectant treatment. In the case of postoperative thrombophlebitis of unknown bacterial origin (Case 207), no appreciable improvement was produced until after 6 days of penicillin treatment.

The patient with acute mastoiditis associated with suppurative otitis media responded by a fall of temperature to normal within 24 hours, but she continued to have a drainage of purulent material from the ear. At the end of 15 days of oral medication, in which time the patient had ceased being toxic but continued to show drainage, the medication was changed to 30,000 units of penicillin intramuscularly every 3 hours. However, the purulent drainage persisted. By this time the organism isolated from the pus proved to be *B. proteus* rather than the streptococcus originally isolated. Thus, though oral penicillin was able to destroy the hemolytic streptococci of the mixed

infection, it could not, nor could parenteral penicillin, get rid of the accompanying gram negative bacilli.

Toxicity. The only toxic manifestations attributable to the oral penicillin administration was urticaria. This occurred in only 5 known instances in the 580 subjects used for assay or for therapeutic studies. Of these, 4 were relatively mild and disappeared in a day or 2; 1 lasted for 5 days and required epinephrin and antihistamine drugs. Three subjects developed urticaria with crude calcium penicillin, the remaining 2 with purified potassium penicillin. However, since both of these latter patients had previously been given sulfonamide medication and especially since the skin involvement was atypical, their reaction might have been due to the sulfonamide. In 1 instance, the reaction occurred on the 2nd day of administration; in 3 it occurred after the medication was completed, on the 6th or 7th day. In the 5th subject, urticaria occurred 2 weeks after treatment when the patient was given several more tablets for a recurrence of the symptoms of sinusitis.

The total incidence of urticaria is 0.86%, if the assay subjects are included. It is 3.8% if only the 130 therapeutic cases are counted. The incidence is only 1.5% (and these may be spurious cases) in the patients treated with purified preparations of penicillin. These values indicate a lower incidence of skin reactions than the 5.7% reported by Lyons⁴ or the 5.5% by Rostenberg⁵ for parenterally injected penicillin. The low incidence may be due to the oral route or to a less antigenic potentiality of purified preparations of penicillin. The latter appears to be the case, since in a study of purified preparations given parenterally¹ no urticarial reactions were encountered.

Discussion. The most obvious conclusion from these studies is that orally administered penicillin is therapeutically successful even in serious infections, if a sufficiently high dose is given. This dose is higher than the 25,000 or 50,000 units recommended in the package descriptions

found with the commercially available oral penicillin. Such doses, even at 2 hour intervals will not produce more than 0.06 unit per cc. most of the time, and may frequently yield only 0.03 unit or less per cc. On the other hand, 100,000 units, especially after an initial "booster" dose of 200,000 units tend to produce 0.125 unit or more per cc. for at least 2 hours and most often 0.06 unit in the 3rd (and sometimes 4th) hour. Such levels should be effective against infections by most of the organisms regarded as sensitive to penicillin.

The clinical results in 49 cases of pneumonia and 81 cases of miscellaneous infections bear out this impression. In 77% of the cases of pneumonia, subsidence of fever and toxic symptoms occurred within 48 hours. Many of these patients actually showed a critical drop in temperature during the first 12 hours, a result as good as any obtained with parenterally injected penicillin. Of the remaining 23%, some had complicating involvements due to virus or penicillin-resistant bacterial infections. Similar results were found in the miscellaneous group, especially when the organism involved was a *Strep. hemolyticus*. Staphylococci infections were usually more resistant but even these responded satisfactorily to oral penicillin.

Since it has been demonstrated that the large majority of patients with acute infections treated orally with penicillin show subsidence of fever and toxic symptoms within 48 hours, failure to achieve such successful therapeutic effect in that period should be the signal for immediate reinvestigation of the clinical features of the case. The reason for failure may be one of the following: 1. Penicillin has been inadequately absorbed or its administration for other reasons has unexpectedly produced low plasma concentration. This phenomenon occurred in a few of our cases.

2. The illness has not been due to a penicillin-sensitive organism. For example, pneumococcal pneumonia may be simulated by a virus pneumonia.

3. The bacterium involved may be an

unusually resistant strain of what is normally a penicillin-sensitive microorganism.

4. There may be a complication much more difficult to treat than the primary infection. In cases of pneumonia, especially in elderly persons, an accompanying severe bronchitis with a thick tenacious mucopurulent exudation, may require very high concentrations of penicillin for successful management.

If any of these 4 factors are present, the original dose of penicillin will prove to be inadequate. It is recommended, then, if after 48 hours of oral treatment with penicillin no subsidence of fever and toxicity has occurred, that the dosage be doubled or that parenterally administered penicillin be given in doses of 40,000 or 50,000 units every 3 hours. In the meantime the patient should be carefully re-examined for complications, and, at the same time, the offending bacterium should be isolated and tested for penicillin sensitivity. Even if the disease process turns out to be due to a virus infection, the additional penicillin will at least have served to prevent or minimize complications.

The severity of the infection has no relation to the resistance of the offending organism to penicillin. The most serious cases of pneumonia may be produced by pneumococci the growth of which is inhibited by very low concentrations of penicillin. These will usually respond rapidly to the recommended doses of penicillin. On the other hand, mild infections due to a staphylococcus, such as paronychia or furuncles, may require very much higher doses of penicillin than needed for a severe streptococcus sore throat. Similarly, bronchitis due to staphylococci may be much more difficult to treat than lobar pneumonia. Thus, the general recommendation of small doses of penicillin orally, say 25,000 or 50,000 units, for mild infections is fallacious. The criterion for dosage should be only the sensitivity of the organism to penicillin. It would be safer to make the general

recommendation of the dosage used in this study, namely, 200,000 units initially followed by 100,000 units every 3 or 4 hours. Our most recent experience indicates that after the critical fall in temperature has occurred there is probably little danger in giving 200,000 units for the 8 hour sleep period and returning to 100,000 units every 4 hours for the remaining period of the day.

Summary. 1. Forty-nine patients with pneumococcal lobar pneumonia and 81 patients with miscellaneous infections produced by penicillin-sensitive organisms were treated with several preparations of penicillin orally administered in primary doses of 200,000 units followed by 100,000 units every 3 hours.

2. In 77% of the cases of pneumonia, subsidence of fever and toxic symptoms occurred within 48 hours, some within 12 hours. Of the remaining 23%, failure was due to (a) inadequate absorption of penicillin, (b) the presence of a penicillin-insensitive organism such as a virus, (c) penicillin-resistant pneumococci, or (d) overwhelming complications.

3. The patients with miscellaneous infections responded similarly well to oral management with penicillin, those with hemolytic streptococci rapidly and those with staphylococci more slowly. The results were comparable with our experience with parenterally administered penicillin.

4. The plasma penicillin levels under this regimen were usually 0.06 unit per cc. or higher during most of the 3 hour interval between doses, as had been anticipated from assays.

5. Urticaria occurred in 3.8% of the 130 therapeutic cases and only in 0.86% of the 580 total subjects used for either assay or treatment. When purified preparations were used, only 2 spurious cases of urticaria developed.

6. The severity of the infection has been found to have no relation to the penicillin dosage required. Only the sensitivity of the organism to penicillin should be the determining factor in dosage.

7. Crude calcium penicillin in capsules gave the poorest therapeutic results. For the other preparations used, there was no considerable difference in the results obtained.

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THE SEROLOGIC RESPONSE FOLLOWING PENICILLIN THERAPY FOR
EARLY SYPHILIS*†

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THE evaluation of a new antisyphilitic agent is an arduous time-consuming, and painstaking procedure. Before clinical trial in human infection is justified the drug must have been demonstrated in the laboratory to be both therapeutically efficacious and nontoxic. In the final analysis, therapeutic efficacy is measured in human infection in terms of clinical and serologic cure. This is determined in early syphilis by the absence of relapse (clinical and/or serologic), of seroresistance, and of late progression in large numbers of patients followed after termination of treatment for prolonged periods, probably a minimum of 5 years.¹² There are, however, in early syphilis immediate indicators of therapeutic adequacy which permit preliminary evaluation in shorter periods of time: the disappearance time of *T. pallida* from superficial lesions, the rapidity of healing of early manifestations, the serologic response measured by quantitative methods, and the outcome of pregnancy in syphilitic females.

Since the original demonstration of the treponemicidal action of penicillin by Mahoney, Arnold, and Harris,⁷ much has been accomplished through cooperative effort^{10,14} toward the evaluation of this

new chemotherapeutic agent in syphilis. In this instance, because of the urgency of war and the almost complete absence of toxicity, clinical trial in man has proceeded simultaneously with experimental trial in the laboratory. The rapidity of disappearance of surface organisms and of healing of visible lesions compares favorably with previously used therapeutic agents. Preliminary reports^{10,8,1} suggest that the initial serologic response is satisfactory, but data comparing the serologic response following penicillin therapy with that under previously established methods of treatment have not yet been presented. It is the purpose of this report to provide information with respect to this pertinent point.

Material and Method. The distribution by race, sex, and age of the 208 patients comprising this material is indicated in Table 1. Only patients presenting previously untreated primary or secondary syphilis who submitted to hospitalization for treatment with penicillin between Sept. 28, 1943 and Dec. 1, 1945 are considered in this report. The diagnosis was confirmed in each instance by darkfield demonstration of *T. pallida*. Additional studies performed on each patient before

* The work described in this paper was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Washington University.

† The Chairman of the Advisory Committee to the National Institute of Health Syphilis Study Section has suggested that publications of the cooperative study of penicillin in syphilis be prefaced by the following statement: "The results which are to be presented in this paper must be interpreted in light of the fact that from June 1943, the date of inception of the study, to the present, commercial penicillin has been a changing mixture of various substances. The content of 'impurities' has gradually decreased as potency, in terms of units per mgm., has increased. The relative amounts of the several identified penicillin fractions G, F, X, and K, have likewise varied from time to time. Those two changes, and perhaps others, suggest that therapeutic efficacy may not have remained constant; and that it may be significantly different today than it was originally. It is not now possible to assess the extent to which these changes may have affected the results here reported."

treatment included a quantitative blood serologic test for syphilis (Kahn) and an examination of the cerebrospinal fluid (cell count, total protein determination, colloidal test, and Kolmer Wassermann). Penicillin was administered to approximately 90% of the patients in this series by one of the 3 following schedules: (1) 1.2 million Oxford units (total dosage) in $3\frac{3}{4}$ days (51 patients), (2) 1.6 million units in 10 days (73 patients), and (3) 4.8 million units in $7\frac{1}{2}$ days (58 patients).^{*} The sodium salt was employed exclusively, equally divided doses being injected intramuscularly every 3 hours.[†]

from consideration when either clinical relapse, or the initial evidence of a subsequently confirmed serorelapse occurred.

Data collected in this manner are presented to show: (1) the serologic response following penicillin in comparison with that during the first 8 weeks of prolonged weekly arsenical and bismuth therapy and, (2) the serologic response following penicillin therapy during the first year after treatment according to duration of disease, race, sex, age, and outcome of pre-treatment spinal fluid examination.

For the comparisons, 2 studies were selected from the literature which illustrate

TABLE 1.—DISTRIBUTION OF 208 PATIENTS WITH EARLY SYPHILIS BY RACE, SEX, AND AGE^{*}

Age (years)	Negro		White		Total
	Males	Females	Males	Females	
Under 20	13	33	1	6	53
20-24	14	20	10	20	64
25-34	23	9	20	16	68
35 and over . . .	8	1	6	8	23
Total	58	63	37	50	208

After completion of therapy, patients were instructed to return at semi-monthly intervals for the initial 3 months and monthly thereafter during the first year of post-treatment observation. Clinical and quantitative serologic examinations were performed on each return visit. The quantitative blood serologic titer was determined by the Kahn technique and recorded in Kahn units.^{6†} For the purpose of this study patients were withdrawn

the serologic response during the first 8 weeks of arsenical therapy administered by prolonged methods (weekly injections). In one of these, Moore, Stanton, Robinson, and Eagle¹¹ present the serologic responses observed during therapy with five different arsenical drugs (arsphenamine, neoarsphenamine, silver arsphenamine, bisarsen, and mapharsen) in terms of average subsequent titers[§] as compared with pre-treatment titers. In the other, Crosby and

^{*} The remaining 10% were treated over similar time-periods but with varying total dosages.

[†] The relatively small number of patients treated by these several methods preclude in this report a study of the effect of individual schedules. In the cooperative study,¹⁰ no difference was noted in the serologic response with total dosages varying from 300,000 to 1.2 million units; with 60,000 units the rate of fall of serum reagin appeared to be retarded.

[‡] This method of quantitation, as described by Kahn and as used in this study, is as follows: "A definitive precipitate (+ + + +, + + +, or + +) is recorded as positive, while a very weak reaction is discounted. If a serum gives a + + + +, + + +, or + + reaction in an undiluted state only and is negative in the dilution series, it is considered as containing Kahn units as indicated by the plus-signs (4 units, 3 units, or 2 units respectively). The potency of any serum which is positive on dilution is determined according to the formula $S = 4 D$, where S is the serum potency in terms of Kahn units and D is the highest dilution ratio giving a positive (+ + + +, + + +, or + +) reaction. Thus if serum dilution 1:5 is positive and 1:10 and higher dilutions are negative, the serum contains 5×4 or 20 Kahn units."

[§] In this method of analysis, the average (mean) pre-treatment titer is assigned the value of 100, and at each subsequent observation the average titer is expressed in terms of per cent of the original. The quantitative method used by Moore et al. was a complement-fixation technique, results being expressed in dilution units.

Campbell² used median titers* to portray the serologic response of patients during weekly treatment with the arsenicals (without distinction between the several drugs) according to the stage of disease at onset of treatment.

The latter method is used also in the second part of this paper to demonstrate the serologic response during the first year following penicillin therapy.

positive primary or early secondary syphilis during weekly treatment. Superimposed on this graph is the result following penicillin therapy in 190 patients in the same diagnostic categories. It is clear that the rates of fall of serum reagin during weekly treatment with the arsphenamines (old arsphenamine, neoarsphenamine, silver arsphenamine, bismarsen) and with arsenoxide (mapharsen) are essen-

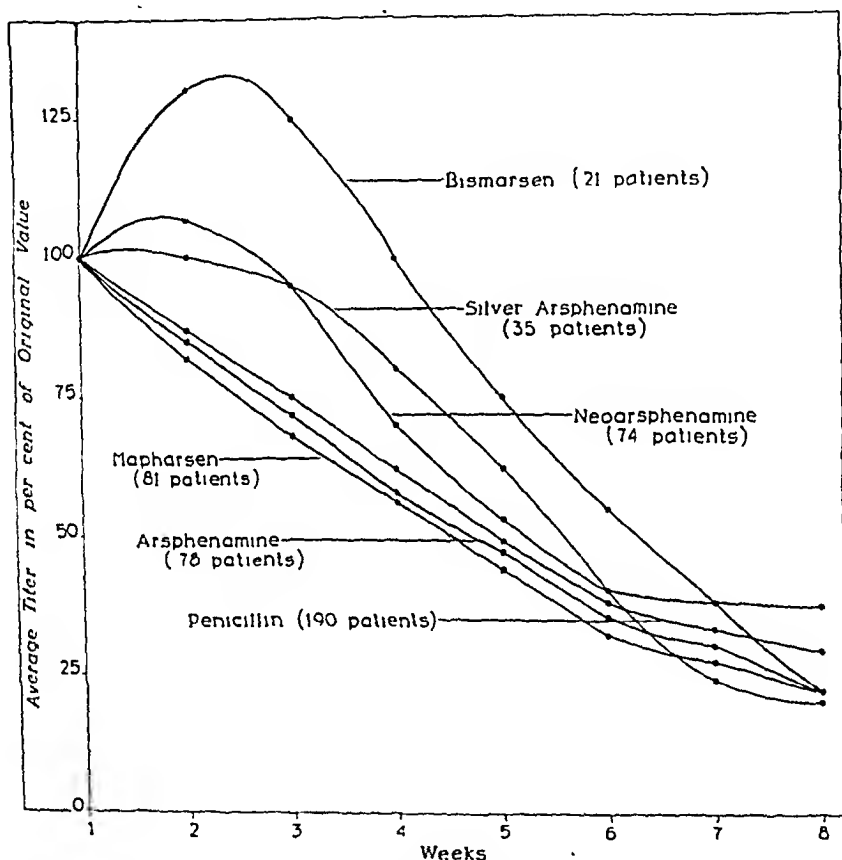


FIG. 1.—Comparison of serologic response in early syphilis during treatment with the arsenicals and following penicillin. (After Moore, Stanton, Robinson and Eagle, *Am. J. Syph. Gonorr. and Ven. Dis.*, courtesy of C. V. Mosby Co.)

1. Comparison of Serologic Response During the First Eight Weeks of Arsenical Therapy and Following Penicillin.

(a) *With Different Arsenical Drugs.* The number of patients treated with each of five drugs and the observed serologic trends are indicated in Fig. 1, taken from the first report,¹¹ of 289 patients with sero-

tially similar, and that, by this method of comparison, the serologic response following penicillin therapy over this time-period does not differ materially from the other agents.

(b) *By Stage of Disease.* In Figs. 2-4 the serologic response following penicillin therapy is compared with the results

* Medians are used rather than the averages (means), since these values, above and below which there are an equal number of observations, give a more representative description, not being thrown far in one direction or the other by extremely high or low observations. These median values are plotted on arithlog paper in order to portray the rate of change of one line in respect to others.

depicted by Crosby and Campbell² in their study of patients according to stage of disease.

A comparison of the serologic response in seropositive primary syphilis during the first 8 weeks of arsenical treatment and that following penicillin therapy is shown in Fig. 2. The median pretreatment complement-fixation dilution titer (120) is considerably higher than the corresponding Kahn titer (40), but at the end of 4 weeks the figures are identical and

in the penicillin treated patients becomes accelerated and the trends for the last two weeks are similar.

A delay in the rate of fall of serum reagin following penicillin therapy appears even more pronounced in patients with late secondary syphilis* (Fig. 4). Although before treatment the median titers were identical, at the end of 8 weeks the median titer of the penicillin treated group has declined only 50% as compared to an 85% fall in the arsenical treated patients.

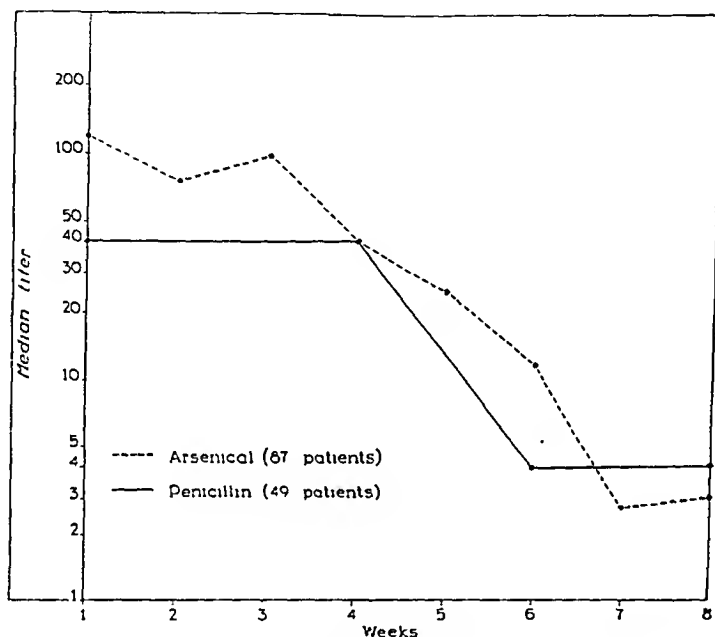


FIG. 2.—The serologic response in seropositive primary syphilis result of penicillin compared with arsenical therapy.

remain essentially the same through the 8th week. The over-all serologic trends of the two treatment methods suggest that, in this comparison, the response following penicillin may be slightly less prompt over this time-period than that recorded during arsenical treatment.

In early secondary syphilis* (Fig. 3) the rate of fall of serum reagin following penicillin therapy appears to be retarded initially in comparison with that during treatment with the arsenicals. After the 6th week, however, the serologic response

The significance of these comparative trends is discussed in a subsequent paragraph.

2. Serologic Response During the First Year Following Penicillin Therapy for Early Syphilis.

(a) *By Stage of Disease.* For the purpose of comparison with arsenical therapy the foregoing graphs depicted the results of only the first 8 weeks following penicillin therapy. The eventual serologic outcome of the penicillin treated patients in relation to stage of disease at the onset of

* Secondary syphilis has been divided arbitrarily into early (duration of secondary lesions 21 days or less) and late (duration of secondary lesions 22 days or more).

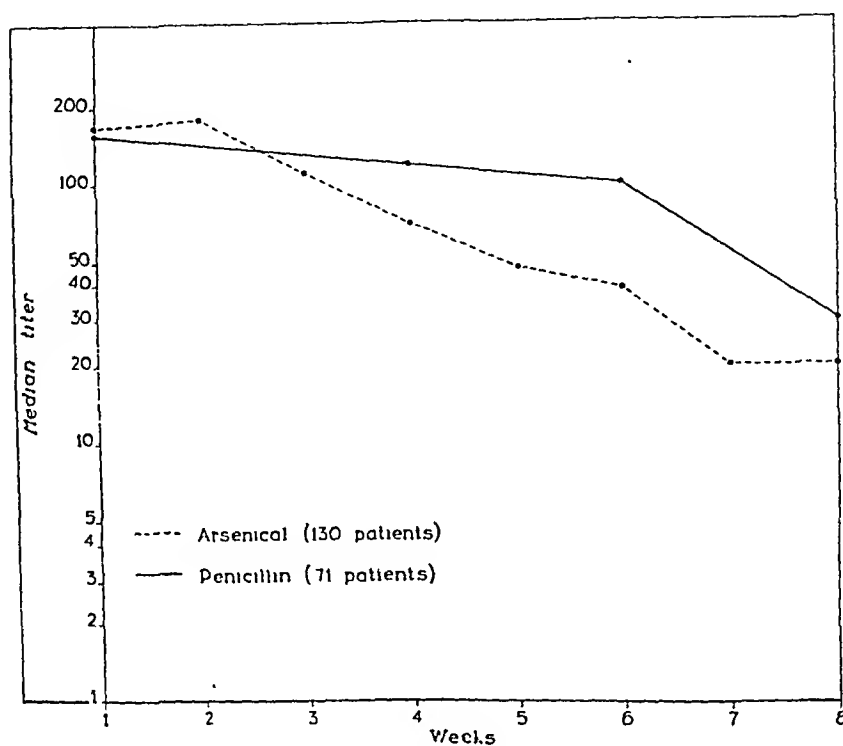


FIG. 3.—The serologic response in early secondary syphilis* result of penicillin compared with arsenical therapy.

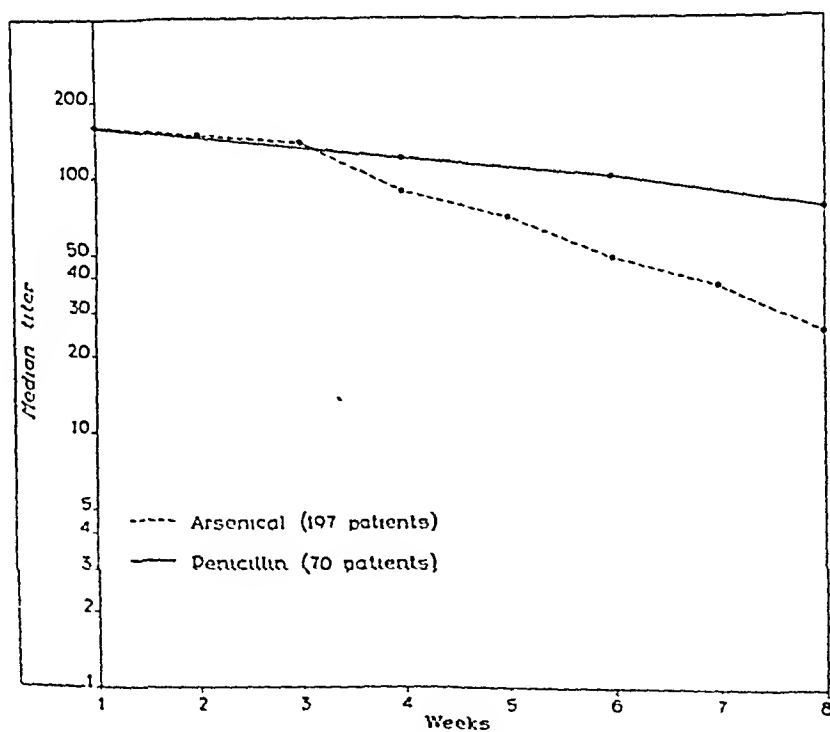


FIG. 4.—The serologic response in late secondary syphilis† result of penicillin compared with arsenical therapy.

* Early secondary syphilis—duration of secondary lesions 21 days or less.

† Late secondary syphilis—duration of secondary lesions 22 days or more.

treatment is shown in Fig. 5. (The number of observations on which this and the following graphs are based is indicated in Table 2). As depicted in the graph, the serologic trends, as indicated by the degree of declivity of the lines, for seropositive primary syphilis and early secondary syphilis appear to be roughly parallel, the median pre-treatment Kahn titers being 40 and 160 respectively, while the interval between the beginning of treatment and permanent seronegativity was 16 weeks for seropositive primary syphilis and 24

In the light of these combined results, it would appear that the time interval between onset of treatment and seronegativity is dependent upon duration of disease as well as upon the original height of the titer. This observation corresponds with clinical experience, the longer the duration of disease, the longer the period to serologic negativity.

(b) *By Race and Sex.* The modifying effect of race and sex on the course of syphilitic infection is too well known to require documentation. The propensity

TABLE 2.—NUMBER OF OBSERVATIONS ON WHICH GRAPHS ARE BASED*

Fig No	Indicating	No. of Patients	No of Initial Observa	No of Post-treatment Observations in Follow-up Period Terminating at															
				4 wks	8 wks	12 wks	16 wks	20 wks	24 wks	28 wks	32 wks	36 wks	40 wks	44 wks	48 wks				
5	<i>Stage of Disease</i>																		
	Seropos. prim. syphilis . . .	49	49	26	56	55	30	22	23	21	16	15	9	11	10				
	Sec. syphilis—duration																		
	21 days and under . . .	71	66	25	91	58	39	35	31	28	27	17	18	17	14				
	Sec. syphilis—duration																		
	22 days and over . . .	70	66	23	79	60	43	32	28	17	15	14	15	14	10				
6	<i>Race and Sex</i>																		
	C M	58	56	25	68	54	32	18	21	15	13	12	9	12	9				
	C F	63	61	18	74	58	36	38	36	25	22	18	17	14	14				
	W M	37	36	13	47	32	21	15	8	14	9	8	5	8	7				
	W F	50	49	24	60	41	25	28	23	18	20	15	13	14	11				
7	<i>Age Group</i>																		
	Under 20	53	50	13	61	45	30	27	26	19	14	13	9	12	9				
	20-24	64	61	25	73	64	30	28	26	22	19	15	12	12	7				
	25-34	68	68	32	86	63	36	32	24	24	24	16	16	15	20				
	35 and over	23	23	10	30	18	17	12	11	8	7	7	8	9	5				
8	<i>CSF†</i>																		
	Normal	143	137	46	158	133	84	67	54	45	38	29	28	27	25				
	Abnormal	62	57	34	79	53	28	28	30	27	24	18	15	20	13				

* The presence in certain of the follow-up periods of more observations than of original patients is due to multiple visits by the same patients.

† Cerebrospinal fluid.

weeks for early secondary syphilis. With late secondary syphilis, although the median pre-treatment titer corresponds with that of early secondary syphilis, the decline of titer was slower, and permanent seronegativity was delayed until the 36th week. These results correspond, in general, with those of Crosby and Campbell. In their material, the serologic response for seropositive primary syphilis was accelerated in comparison with that for early secondary syphilis. Between early and late secondary syphilis the delay in the serologic response of the latter was less evident than in the present material.

for late syphilis in the Negro to involve the cardiovascular and osseous systems in contrast to the predominance of neurosyphilis in the white race is well recognized, as is the milder course of syphilis in females as compared to males. Crosby and Campbell found no significant difference in the serologic response during the first eight weeks of arsenical treatment in respect to race and sex, but did not report more prolonged observations. In the present study, however, it is possible to determine eventual serologic tendencies, as shown in Fig. 6. No marked difference is apparent in the serologic response be-

tween males and females of the white race, and the trend in Negro male patients does not differ significantly from that of white males. It is true that the median pre-treatment titer of white females was higher than either of the male groups and

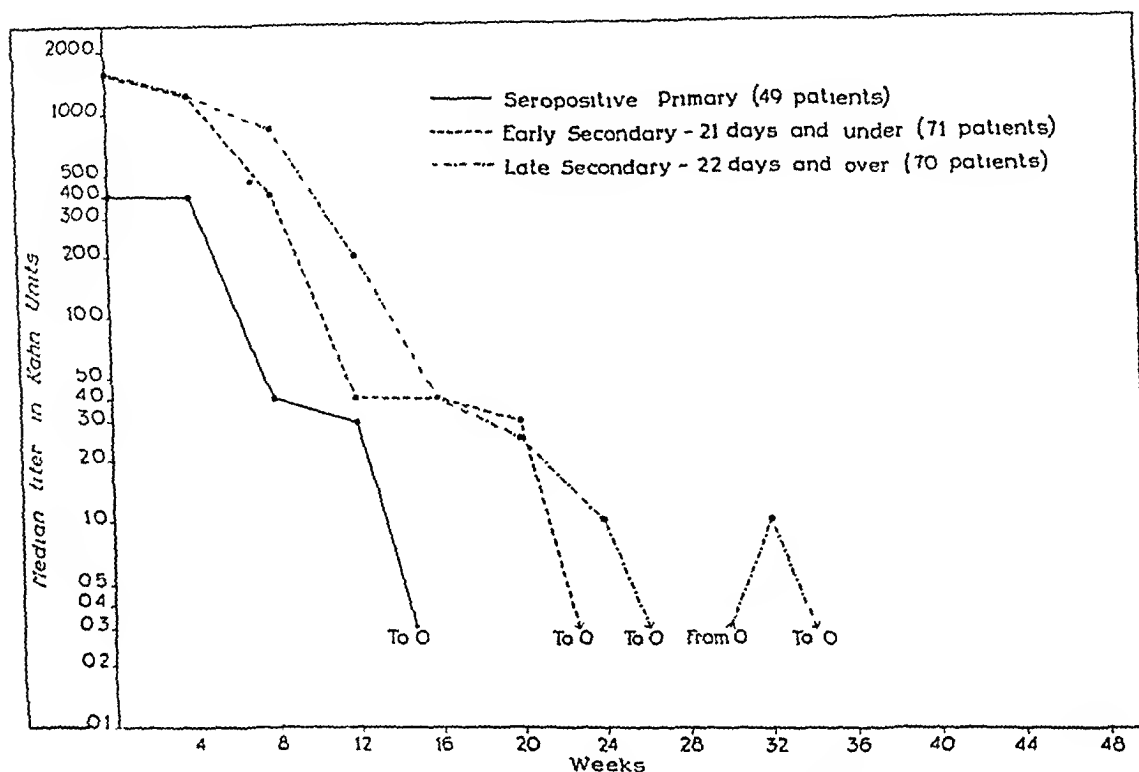


FIG. 5.—Serologic response following penicillin therapy for early syphilis by stage of disease.

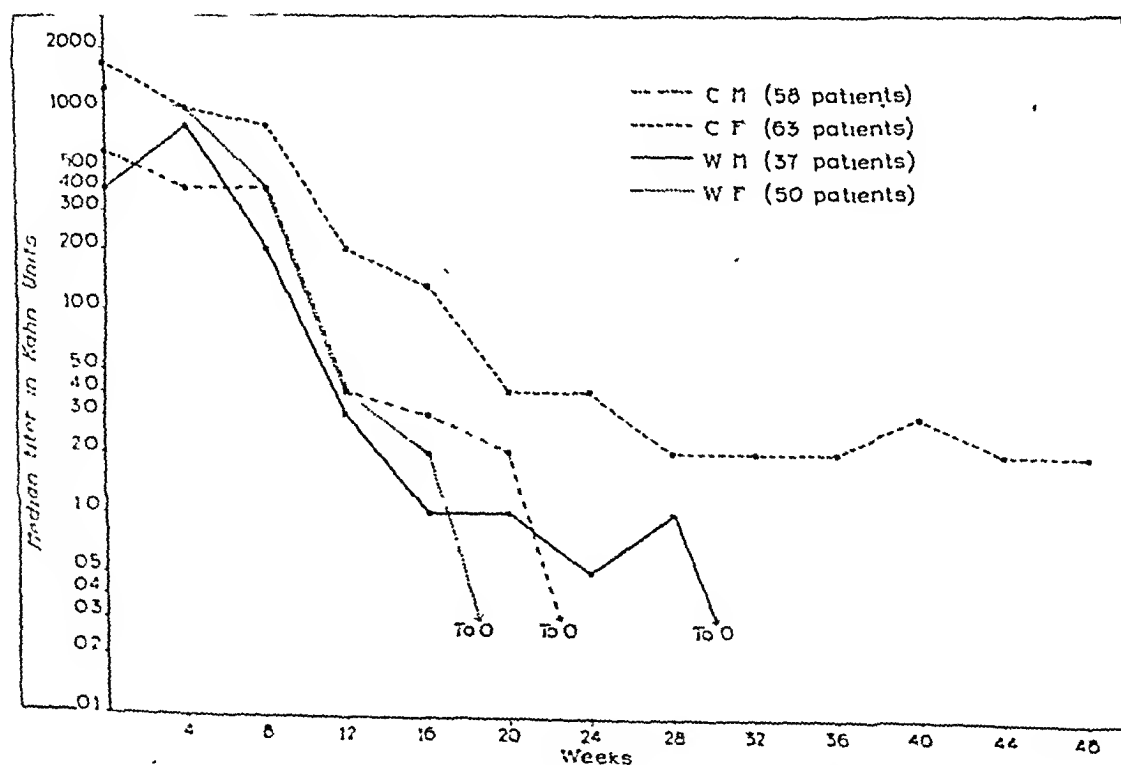


FIG. 6.—Serologic response following penicillin therapy for early syphilis by race and sex.

that the former attained seronegativity more promptly than either of the latter. However, the striking feature of this graph is the retarded rate of fall of serum reagin in Negro females, this group remaining seroresistant through the 48th week of post-treatment observation.*

(c) *By Age.* The serologic trends of the four age groups (under 20, 20-24, 25-34, and 35 and over) into which this material has been divided is portrayed in Fig. 7.

The blood serologic response of patients with normal and with abnormal pre-treatment spinal fluids† is presented in Fig. 8. Although the initial response of the patients with early asymptomatic neurosyphilis appears slightly retarded, this is probably not significant since the over-all trends are identical. This observation is in agreement with the study of Crosby and Campbell, who found no difference in blood serologic response dur-

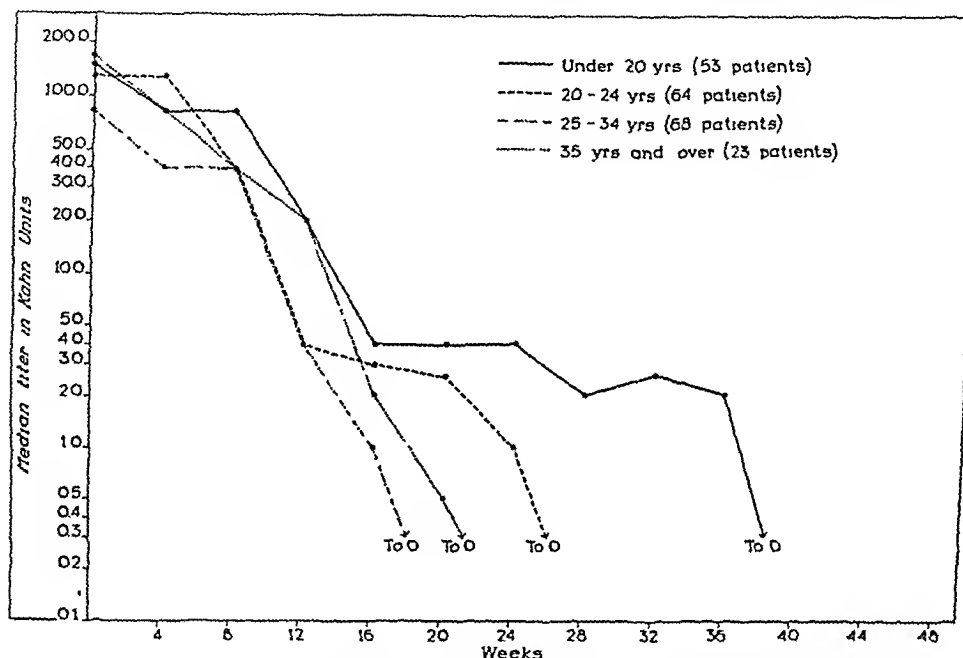


Fig. 7.—Serologic response following penicillin therapy for early syphilis by age.

The most prompt serologic response is recorded in the 25-34 years age group, the slowest in the under 20 years group, and the remaining two groups are intermediate.

3. *The Influence of Early Asymptomatic Neurosyphilis on the Serologic Response Following Penicillin Therapy for Early Syphilis.*

* It should be pointed out that the serum reagin level persisting from the 28th through the 48th week (2-3 Kahn units) corresponds to the "doubtful" range with qualitative serodiagnostics tests.

† Arbitrarily, cerebrospinal fluids with any one of the following changes have been classified as abnormal—cells over 6 per cubic millimeter, total protein over 40 mgms. per cent, colloidal test with a reading of over 2 in any tube, complement-fixation test doubtful or positive in maximum amounts of spinal fluid or less.

‡ Fluids were tested after 6 months of treatment rather than prior to treatment as in the present study.

ing the first 8 weeks of arsenical treatment between 30 patients with abnormal and 496 with normal spinal fluids.‡

Discussion. The difference in the statistical methods used may account for the apparent disparity in results when our material is compared with that of Moore, Stanton, Robinson, and Eagle on the one hand and when it is compared with that

of Crosby and Campbell on the other. In the former (according to drug used), the serologic trends appear to be essentially similar, while in the latter, compared by stage of disease, there is an apparent retardation in the serologic response following penicillin. Moore *et al.*, using mean (average) values, assigned arbitrarily the value of 100 to the mean pre-treatment titer and computed subsequent titers in terms of per cent of the original. These results were plotted on arithmetic graph paper. The method of Crosby and

accomplishes the same purpose as the use of arithlog graph paper for actual values. In any graphic comparison of serologic trends it must be remembered that the actual rate of fall (the degree of declivity of the lines) is *predetermined* to a large extent by the dilutions of the serum routinely tested by whatever quantitative technique employed. For example, if a quantitative test is performed on serially two-fold diluted serum (this is the procedure usually followed), unless interpolation is performed, the reagin titer of each

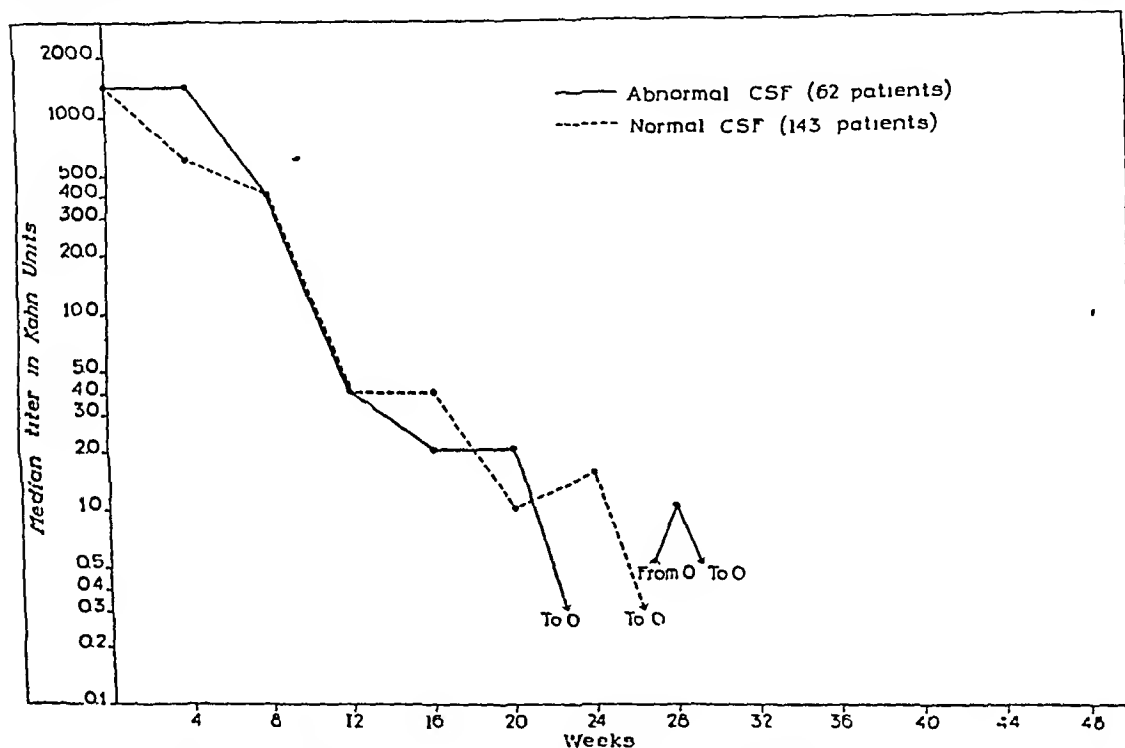


FIG. 8.—Serologic response following penicillin therapy for early syphilis effect of early asymptomatic neurosyphilis.

Campbell used median rather than mean titers, these being plotted directly on arithlog graph paper. The former statistical method may be preferable for the purpose of comparing trends of different tests since it is less affected by serologic vagaries, although it has all the disadvantages of the use of averages rather than of medians as centering values. The chief advantage is the common starting point of the trend lines. The use of percentages of this value for subsequent points plotted on arithmetic graph paper

successive tube can be only 100% greater than the preceding one (4, 8, 16, 32, etc.); and conversely, decreasing titer can only be 50% if slight (one tube), 75% if greater (two tubes), and 87.5% (three tubes) etc. (32, 16, 8, 4, etc.). Thus, under these circumstances, only gross comparisons can be made, since slight differences are not apparent.

There are 3 other technical factors which render difficult comparisons of serologic results: (1) variations in sensitivity of the tests; (2) differences in

methods of reporting results (units); and (3) differences in interpretation of degree of positivity (defining the end-point in quantitative techniques).

The importance of variations in sensitivity which are inherent in all serologic tests for syphilis, although recognized by serologists and syphilologists alike, cannot be too repeatedly emphasized. This factor obtains not only in comparisons between two different serologic techniques (one flocculation as compared with a second flocculation test; or, a complement-fixation technique as compared to a flocculation test) but also when the same technique is performed in two different laboratories, and, because of unavoidable day to day variation in sensitivity, even when the same technique is performed in a single laboratory.

In the present study, a quantitative flocculation technique was employed in contrast to the quantitative complement-fixation procedure used by Crosby and Campbell. The latter technique, although inherently more sensitive than the flocculation test, is *less* sensitive than the former in sera of low reagin content because of a constituent of serum which inhibits complement-fixation in low dilutions.³ In sera of high reagin content (high-titered), on the other hand, the effect of this serum inhibitor is nullified by dilution and the resulting (by dilution) small amounts of reagin remaining are more readily detected by complement-fixation techniques. Therefore, titers determined by complement-fixation methods under such conditions are higher than with flocculation techniques. Considering this factor alone (*i.e.*, disregarding the Kahn method of expressing units of serum reagin in multiples of the dilution) it would be anticipated that the pre-treatment titers obtained by Crosby and Campbell in general would be higher* and the serologic decline more precipitous than in the present study.

The second factor affecting the present comparisons is the differing methods of reporting units of serum reagin. Crosby and Campbell expressed the quantitative titer in *dilution units*† while in the present study results are expressed in *Kahn units* (approximately four-fold greater than dilution units‡). This factor considered alone would tend to make the original titer higher in our material. This difficulty could be eliminated if serologists would uniformly express quantitative results in dilution units, a standard practice in reporting results of other serum tests of antigen-antibody reactions.

The third technical factor is concerned with the definition of the end-point in quantitative techniques. In the Kahn technique (the present study) 2+ is read as positive⁶ whereas in the complement-fixation technique of Crosby and Campbell's study 2+ was considered as doubtful.⁴ The total influences of these factors (complement-fixation *vs.* flocculation technique, dilution units *vs.* Kahn units, and the varying definitions of the end-point) on comparisons of serologic response are difficult of evaluation. The interpretation of comparative trends, therefore, must be considered in the light of these indicated complexities.

In view of the correlation between the serologic response in early syphilis following penicillin therapy and that during treatment with the several arsenical drugs reported by Moore, *et al.*, it would appear that, with any effective treatment method (or drug) the rate of fall of serum reagin is essentially constant. Since, as pointed out by the previous authors in reference to the arsenicals, these several antisyphilitic agents are not equally therapeutically efficacious as judged by ultimate clinical outcome, it is apparent that the quantitatively measured serologic response, while of value, is not an important criterion of therapeutic efficacy.

* Except in low-titered seropositive primary syphilis.

† With this method, serologic titer is expressed in terms of units of reagin corresponding to serum dilution. Thus, if a given serum is positive in a dilution of 1:2 (1 part of serum and 1 part of isotonic saline) and negative in higher dilutions, it is said to contain 2 units of reagin. Similarly, if positive in a dilution of 1:100 but negative with higher amounts, it is said to contain 100 units, etc.

‡ See footnote page 356.

Another consideration in comparative studies of serologic response following treatment for early syphilis is the similarity of the basic material. Comparisons are not valid unless there is a similar distribution of patients by stage (duration) of disease. The effect of duration of infection in early syphilis on ultimate clinical outcome has been emphasized recently by Eagle⁵ and confirmed by the Penicillin Panel¹⁰ who, in contrast to previous observers,¹³ found an increased incidence of relapse in secondary as compared to seropositive primary syphilis.

it would be anticipated that the incidence of asymptomatic neurosyphilis would increase proportionately with increasing duration of infection. It is surprising, therefore, that the prevalence of abnormalities in the cerebrospinal fluid is almost identical in the four groups (seronegative primary, 28%; seropositive primary, 27%; early secondary, 25%; late secondary, 29%). In regard to the type of treatment (this is most easily measured in terms of duration*) there are no significant differences between the four stages of disease. Since patients who subsequently relapsed

TABLE 3.—IMPORTANT VARIABLES ACCORDING TO STAGE OF DISEASE

Stage of Disease	Number of Patients	Abnormal CSF Per cent With	Duration of Treatment (Days)			Observed Relapse Per cent
			3½	Per cent in 7½	10	
Seronegative Primary . . .	18	28	22	50	28	17
Seropositive Primary . . .	49	27	20	51	29	10
Early Secondary . . .	71	25	21	52	27	10
Late Secondary . . .	70	29	19	49	33	6
Total . . .	208	27	20	50	29	9

TABLE 4.—IMPORTANT VARIABLES ACCORDING TO RACE AND SEX

Race and Sex	Number of Patients	Seroneg. Prim.	Stage of Disease Per cent with			Abnormal CSF Per cent With	Duration of Treatment (Days)			Observed Relapse Per cent
			Seropos. Prim.	Early Sec.	Late Sec.		3½	Per cent in 7½	10	
Negro, Male . . .	58	16	29	24	31	26	17	53	29	7
Negro, Female . . .	63	3	8	44	44	22	24	48	28	11
White, Male . . .	37	16	43	22	19	38	19	51	30	11
White, Female . . .	50	2	22	42	34	26	20	50	30	8
Total . . .	208	9	24	34	34	27	20	50	30	9

From Fig. 5 the observation was made that the longer the duration of the disease, the longer the period to serologic negativity following treatment. Before accepting this observation as valid, other factors which might account for the observed difference in serologic behavior deserve consideration: (1) the incidence of asymptomatic neurosyphilis; (2) the efficacy of the treatment schemes employed; and (3) the incidence of subsequent relapse in the respective groups. Data pertaining to these are presented in Table 3. *A priori*,

are included in the serologic trends until either clinical relapse† or the initial evidence of a subsequently confirmed serorelapse occurred, it is important to determine the extent to which each group under consideration is weighted with those patients who ultimately relapsed. Relapse subsequently occurred in 10% of patients with seropositive primary syphilis, in 10% with early secondary syphilis, and in 6% with late secondary syphilis. Thus, this factor could not have contributed to

* As judged by ultimate relapse, the least efficacious of these 3 treatment schedules appears to be the shortest in duration (3½ days). There is as yet no clear-cut difference between the 7½ and 10 day schedules.

† Because of the difficulty of differentiating reinfection from relapse, the reappearance of infectious lesions following treatment has been considered a treatment failure, i.e., relapse.

the observed serologic response.* It would appear, therefore, that duration of infection *per se* accounts for the retardation in rate of fall of serum reagin.

Other factors are apparently of less importance in regard to serologic response. In Fig. 6 it was noted that Negro females seemed to remain seroresistant longer than other race and sex groups. Other related factors are studied in Table 4. It is seen that (1) a higher proportion of Negro females (44%), had late secondary syphilis, *i.e.*, longer duration of infection, than any of the other groups, (2) a higher proportion of Negro females (24%) than of any of the other groups received the shortest and presumably the

These differences may not be significant, yet it is of importance to determine whether factors existing in the basic material (Table 5) can account for the observed variations. The group which showed the slowest response in Fig. 7 (under 20) was composed of 62% Negro females. Seventy-eight per cent were patients with secondary syphilis. The 35 and over age group contained slightly but not significantly more late secondary syphilis than the youngest age group. The age group showing the most prompt response (25-34 years) had the highest proportion of patients with primary syphilis. The presence of abnormalities in the cerebrospinal fluid again did not seem to influence

TABLE 5.—IMPORTANT VARIABLES ACCORDING TO AGE

Age Group (years)	Number of Patients	Race and Sex Per cent With					Seroneg. Prim.	Stage of Disease Per cent With			CSF Per cent With	Duration of Treatment (days) Per cent in			Observed Relapse Per cent
		CM	CF	WM	WF	Seropos. Prim.		Early Sec.	Late Sec.	3½		7½	10		
Under 20	53	25	62	2	11	9	13	40	38	15	17	57	26	13	
20-24	64	22	31	16	31	9	25	36	30	23	20	48	31	9	
25-34	68	34	13	29	24	10	29	29	31	38	26	46	28	7	
35 & over	23	35	4	26	35	.	26	30	44	30	9	57	35	4	
Total	208	28	30	18	24	9	24	34	34	27	20	50	30	9	

least efficacious treatment schedule, (3) cerebrospinal fluid abnormalities were not related since the Negro female group had the lowest percentage of abnormalities, and (4) subsequent relapse was not an important factor since an equal proportion (11%) of Negro females and white males suffered relapse. Although the longer duration of the disease and the shorter treatment schedule *may* have been concerned in the prolonged serologic response recorded in the Negro female group, it is entirely possible that this is a chance observation based on insufficient data, and that with a larger series of patients this would not hold true.

The effects of age were seen in Fig. 7.

* The proportion of relapses in the 3 diagnostic categories does not correspond with Eagle's much larger experience based on the results of semi-intensive arsenical treatment of 4,823 patients with early syphilis.⁵ In his material, there was a linear relation between relapse and duration of infection, a higher percentage being observed after secondary than after seropositive primary syphilis. In the present material, a total of only 19 relapses (17 mucocutaneous, 2 serologic alone) have thus far occurred. Several of the primary syphilis group classified as relapse, probably if not certainly, represent instances of reinfection. The difference in the incidence of relapse in early and in late secondary syphilis is not significant.

the rate of fall of serum reagin, since the incidence of these abnormalities was highest in the age group showing the most rapid serologic response. Similarly, treatment, measured in terms of duration, seemingly was not concerned in this response. Relapse, in view of its distribution by age groups—under 20, 13%; 20-24, 9%; 25-34, 7%; 35 and over, 4%—may have exerted a retarding influence, since the group with the highest incidence showed the most prolonged response.

From these tables there are no indications that invasion of the central nervous system by *T. pallida* has an appreciable effect on the rate of fall of serum reagin providing treatment has been adequate.

On the contrary, there is evidence both in the present study and in the material of Crosby and Campbell that the blood serologic response is independent of the presence or absence of abnormalities in the cerebrospinal fluid.

Summary. 1. The serologic response during the first year following penicillin therapy is recorded in 208 patients with previously untreated primary or secondary syphilis. Serologic trends are compared with previously published observations during arsenical therapy. The effects of age, race, sex, duration of infection, and asymptomatic neurosyphilis on serologic response are considered.

2. The serologic response observed during the first 8 weeks following penicillin therapy for early syphilis is comparable to that previously reported during weekly treatment with the several arsenical drugs. Since some of these latter agents are known to be therapeutically inferior, this observation reemphasizes the fact that, in the final evaluation of antisyphilitic drugs, serologic response is not an all-important criterion of therapeutic efficacy.

3. In a comparison of the serologic response during the first 8 weeks following penicillin with that previously recorded during weekly arsenical treatment by stage of disease (seropositive primary, early secondary, and late secondary syphilis), an apparent retardation in the rate of fall of serum reagin following penicillin was observed.

4. The serologic trends recorded during

the first year following penicillin therapy provide evidence of a linear relationship between duration of infection and rate of fall of serum reagin—the longer the duration of disease, the slower the serologic response.

5. A study of the serologic response by age, race, and sex demonstrated, in this material, a delayed rate of fall of serum reagin in Negro females and in the youngest age-group (under 20 years). Evidence is presented that the retarded response observed is related (in these groups) to a higher percentage of patients who had (a) longer duration of disease, (b) the least efficacious treatment scheme, or (c) a high incidence of subsequent relapse, or to a combination of these factors.

6. The presence of early asymptomatic neurosyphilis exerted no apparent retarding effect on the rate of fall of serum reagin.

7. The importance of the several factors which influence results in comparative serologic studies is discussed. These include (1) the statistical method of analysis, (2) variations in sensitivity of serologic tests for syphilis, (3) differences in methods of reporting quantitative results and in defining the end-point in quantitative techniques. The lack of correlation in this study between the serologic response following penicillin and that recorded during the first 8 weeks of arsenical therapy when compared (1) by drug and (2) by stage of disease is related to these statistical and technical factors.

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THE ABSORPTION AND ELIMINATION OF SULFADIAZINE ADMINISTERED AS TABLETS, AS A GROUND (MICRONIZED) POWDER AND AS MICROCRYSTALS*

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THAT sulfonamides given by mouth are absorbed to the same extent no matter in what pharmaceutical form they may be administered, is the commonly accepted opinion. Evidence to the contrary has been presented in a few papers, notably that of Reinhold, Phillips and Flippin.³ The report of the work of these authors was published in the August 1945 issue of this JOURNAL, shortly after the experiments to be described below were begun. Reinhold *et al.* have reviewed the pertinent literature, from which they drew the conclusion that it had been shown that "in microcrystalline form the activity (of sulfonamides) is enhanced, but the information available is limited." Describing their own experience with patients from the medical wards of the Philadelphia General Hospital, Reinhold, Phillips and Flippin found that microcrystalline sulfadiazine was absorbed into the blood stream and excreted in the urine more rapidly during the first 6 hours after administration than was sulfadiazine given in tablet form. The experiments to be described herein were performed upon healthy, human volunteers. The results confirm those of Reinhold *et al.* in showing that the smaller the particle size of administered sulfadiazine, the faster the absorption and elimination; at the same time, a considerable body of new data is presented upon the metabolism of these different sized particles of administered sulfadiazine.

Technique. The 3 pharmaceutical forms of sulfadiazine investigated were as follows:

The first consisted of tablets of sulfadiazine purchased on the open market. The second preparation was composed of micronized sulfadiazine suspended in an aqueous vehicle, containing volatile oils, flavoring and coloring agents. This material was prepared by the Pitman-Moore Company of Indianapolis and consisted of sulfadiazine which had been reduced to small spheres, somewhat larger in size than the microcrystals, by a process of grinding. The actual composition of the suspension was described to us as follows: sulfadiazine 10.12 gm., oil of orange 0.002 ml., amaranth 0.0038 gm., sitro or lemon yellow 0.0094 gm., citric acid 0.128 gm., benzoic acid 0.25 gm., kelgin q.s., sucrose 23.97 gm. and distilled water to 100 ml. Reinhold *et al.* found that sugar and flavoring agents had no appreciable effect of themselves upon the absorption and elimination of sulfadiazine, so that the effect or lack of effect of the vehicle and suspending medium was not investigated in the present work. The third preparation consisted of microcrystalline (semi-colloidal) sulfadiazine suspended in the same medium as the micronized material, the size of the microcrystals being of the same order as those employed by Reinhold *et al.* in their suspension. Both of these latter preparations were provided us by the Pitman-Moore Company and we are also indebted to the same Company for a grant-in-aid of this research.

Each preparation was given to a total of 30 healthy, human volunteers, in a dose containing 4 gm. of the drug, at 10 A.M. on the morning of an experiment. At the same time, the volunteers drank 1 pint of water. At intervals of 0.5, 1, 2, 4 and 6 hours after administration of the drug, a

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sample of oxalated blood was obtained as well as the volume of urine which had accumulated during the several intervals. Total and free (and by difference, combined) sulfadiazine were estimated upon an aliquot of whole blood and upon an aliquot of the oxalated plasma, at each interval. The volume of urine was noted and total, free and combined sulfadiazine determined upon each sample before and after centrifuging. The method used for estimating sulfadiazine was a slight modification of the technique of Bratton and Marshall.¹ Upon each sample of urine, a test for albumin was made and the pH determined with the aid of a Coleman pH electrometer. The centrifuged specimen of urine was examined microscopically for crystals of acetylated sulfadiazine, red blood cells, white blood cells and casts. In addition, a close record was kept of the clinical condition of the volunteer with the especial object of detecting any signs of untoward reactions or toxic effects.

The experiments were rotated so that at any one time, approximately equal numbers of volunteers had been allocated to each of the 3 preparations. The results were tabulated and the means, standard deviations and errors of the means and Pearson's coefficients of variation calculated after the formulæ of Hill.²

and gave higher blood levels of sulfadiazine than did the tablets. Also, the suspension of microcrystals was absorbed more rapidly and produced higher concentrations of the drug in blood than did the suspension of micronized powder or the tablets. In almost all instances, the standard error of the mean difference between blood values at any given interval after administration of the 3 preparations was many times the mean difference, thus making the possibility of the mean difference occurring by chance extremely unlikely. Thus, for example, the standard error of the mean difference at 0.5 hours in the concentration of total sulfadiazine in whole blood after giving tablets *versus* after the micronized powder was about 4 times the mean difference, making the chances approximately 1 in 1000 that the difference could have been due purely to chance. Comparing corresponding values after giving the tablets *versus* the microcrystals at the same interval, the standard error of the mean difference was some 10 times the mean difference. In the instance of the remaining possible comparison of corresponding values at the

TABLE 1.—THE CONCENTRATION OF SULFADIAZINE IN MG. PER 100 ML. OF WHOLE BLOOD FOLLOWING ORAL ADMINISTRATION OF 4 GM. OF THE DRUG IN VARIOUS PHARMACEUTICAL FORMS

Pharmaceutical form	Concentration in whole blood: mean \pm standard error				
	0.5 hr.	1 hr.	2 hrs.	4 hrs.	6 hrs.
<i>Total Sulfadiazine</i>					
Tablets	0.45 \pm 0.06	1.3 \pm 0.17	2.8 \pm 0.21	5.6 \pm 0.41	5.9 \pm 0.46
Micronized powder	0.85 \pm 0.10	1.8 \pm 0.20	3.7 \pm 0.26	6.5 \pm 0.34	6.5 \pm 0.36
Microcrystals	1.30 \pm 0.09	2.7 \pm 0.14	4.5 \pm 0.22	7.1 \pm 0.41	7.1 \pm 0.41
<i>Free Sulfadiazine</i>					
Tablets	0.43 \pm 0.06	1.2 \pm 0.16	3.0 \pm 0.24	5.4 \pm 0.36	5.7 \pm 0.46
Micronized powder	0.87 \pm 0.10	1.6 \pm 0.17	3.6 \pm 0.21	6.2 \pm 0.28	6.1 \pm 0.30
Microcrystals	1.30 \pm 0.08	2.6 \pm 0.11	1.3 \pm 0.16	6.9 \pm 0.32	6.4 \pm 0.33
<i>Combined Sulfadiazine</i>					
Tablets	0.02	0.1	0.2	0.2	0.2
Micronized powder	0.02	0.2	0.1	0.3	0.4
Microcrystals	0.0	0.1	0.2	0.2	0.7

WHOLE BLOOD SULFADIAZINE. Values for total, free and combined sulfadiazine in whole blood have been summarized in Table 1. From the values obtained, it is obvious that the suspension of micronized sulfadiazine was absorbed more rapidly

same interval, that is after micronized powder *versus* after microcrystals, the comparable statistical figure is about 7. Similar calculations were made for the remaining figures given in Table 1, and the probability of the mean difference

being due purely to chance drops to about 1 in 20 only in the instances of whole blood total and free sulfadiazine at 4 and 6 hours.

Values for whole blood combined sulfadiazine were low and variable as would be expected, since it is well known that patients upon sulfadiazine therapy have little combined sulfadiazine in blood and since the value for this fraction is obtained by difference between free and total sulfadiazine, it accumulates the errors involved in both these estimations, thus making the standard deviation of combined sulfadiazine means extremely variable. Hence only the mean values for combined sulfadiazine have been reported in Table 1, since in some instances the mean was actually negative and also the standard error was often greater than the mean. The only significant conclusion which may be drawn from these figures is that values for combined sulfadiazine are low; while there were mean differences following administration of the different preparations of the drug, no statistical significance could be proven for the differences. It is possible that the smaller sized particles of sulfadiazine produce a higher concentration of the combined drug in blood, but many more volunteers per group would be required to prove this statistically.

In general, Pearson's coefficient of variation was high for the initial readings at 0.5 and 1 hour but fell to a mean value of about 25 in most instances at 4 and 6 hours in both whole blood (Table 1) and blood plasma (Table 2). This indicated that while early values for blood sulfadiazine concentration were rather variable, the concentration in each group became more nearly alike after 4 hours. Similar results were obtained with values for sulfadiazine in urine, so that no further reference need be made to Pearson's coefficient of variation.

The *conclusions* to be derived from these results are that sulfadiazine is most rapidly absorbed when administered by mouth in the form of a suspension of microcrystals, somewhat less rapidly absorbed when

given as a suspension of micronized powder and least rapidly absorbed when taken as tablets. After about 6 hours from the time of administration, the concentration of total and free sulfadiazine in whole blood is approximately the same, for all practical purposes, no matter in which pharmaceutical form it has been given. The concentration of combined sulfadiazine in whole blood does not reach appreciable values until 6 hours after administration, when it averages 5 to 10% of the total whole blood sulfadiazine, and while the mean values are higher the smaller the particle size of the administered sulfadiazine, it was not possible to prove a statistically significant difference with the number of samples available.

PLASMA SULFADIAZINE. Corresponding values for total, free and combined sulfadiazine in plasma have been summarized in Table 2. From these results, the same general conclusions may be drawn as were in the instance of whole blood, *i. e.*, that microcrystalline sulfadiazine was absorbed most rapidly, the micronized powder next and the tablets least rapidly, with all concentrations of sulfadiazine in blood plasma tending to approximate each other by the end of 6 hours after administration no matter in which form administered. Almost all concentrations of sulfadiazine in blood plasma were higher than those in whole blood, indicating that during the first 6 hours of the experiment at least, there is more sulfadiazine in plasma than in the red blood cells. There were some differences in the distribution of sulfadiazine between plasma and red blood cells following administration of the 3 pharmaceutical forms of the drug. By comparing the mean of all mean values at the 5 intervals studied, the level of plasma total sulfadiazine was 116% of that of whole blood sulfadiazine following administration of tablets, 143% following administration of the suspension of micronized powder and 129% following administration of the microcrystals. Corresponding values for plasma-free sulfadiazine were 116, 138 and 133% respectively and again

the values for plasma combined sulfadiazine were so variable as to make a comparison of little significant value. While mathematically there was little difference in the distribution of sulfadiazine between blood plasma and the red blood cells following administration of the 3 pharmaceutical forms of the drug, the mean percentage distributions suggest that the drug may be present in plasma in relatively greater concentrations than in the red blood cells following the taking of the smaller sized particles of sulfadiazine.

bled in Table 3. In this table, the results are expressed in mg. of the respective forms of the drug per 100 ml. of urine, and while the volume of urine per stated interval varied a good deal from person to person, the average volume per interval was about the same with each preparation of the drug.

It is apparent that the concentration of total, free and combined sulfadiazine was greater following administration of those preparations which were absorbed the more rapidly into the blood stream.

TABLE 2.—THE CONCENTRATION OF SULFADIAZINE IN MG. PER 100 ML. OF BLOOD PLASMA FOLLOWING ORAL ADMINISTRATION OF 4 GM. OF THE DRUG IN VARIOUS PHARMACEUTICAL FORMS

Pharmaceutical form	Concentration in blood plasma: mean \pm standard error				
	0.5 hr.	1 hr.	2 hrs.	4 hrs.	6 hrs.
<i>Total Sulfadiazine</i>					
Tablets	0 22 \pm 0 04	0 93 \pm 0.13	3 1 \pm 0 23	6 5 \pm 0 64	7 1 \pm 0 80
Micronized powder	1 20 \pm 0 19	2 50 \pm 0.35	4 8 \pm 0 41	9 5 \pm 0.49	9 8 \pm 0 59
Microcrystals	1 70 \pm 0 19	3 20 \pm 0 34	5 6 \pm 0 40	9 5 \pm 0 65	8 9 \pm 0 59
<i>Free Sulfadiazine</i>					
Tablets	0 28 \pm 0 04	0.92 \pm 0.14	3 5 \pm 0 41	6 4 \pm 0 59	7 5 \pm 0 85
Micronized powder	1.00 \pm 0.17	2 10 \pm 0.41	4 6 \pm 0 49	8 8 \pm 0.47	8 9 \pm 0 59
Microcrystals	1 80 \pm 0 18	3 40 \pm 0 29	5 8 \pm 0 33	9 1 \pm 0 52	8 5 \pm 0 50
<i>Combined Sulfadiazine</i>					
Tablets	-0.06	0.1	-0 4	0 1	-0 4
Micronized powder	0 2	0 4	0 2	0 7	0 9
Microcrystals	-0 1	-0 2	-0 2	0 4	0 4

Assuming this to be so, it may be concluded that the oral administration of sulfadiazine in the form of a suspension of microcrystals or micronized powder is followed by more rapid absorption of the drug from the gastro-intestinal tract, higher concentrations in blood plasma, less diffusion into the red blood cells and, as will be shown, more rapid elimination in urine, than the oral administration of sulfadiazine as tablets, at least for the first 6 hours after taking the drug.

CONCENTRATION OF SULFADIAZINE IN URINE. The concentration of total, free and combined sulfadiazine was estimated in uncentrifuged and well-shaken aliquots of urine which had been collected by emptying the bladder at the same intervals that blood was withdrawn, no uncollected urine being voided between these intervals. The mean concentrations and their standard errors have been assem-

This was so until about the 4th hour after which the differences were less marked and consistent. Up to the 4th hour, mean differences in concentration at each interval between those taking the 3 preparations of the drug were of the order of 2.5 to 4 times the standard error of the mean difference.

CONCENTRATION OF SULFADIAZINE IN CENTRIFUGED URINE. It is well known that sulfadiazine, especially in the combined form, is relatively insoluble in urine. Since the 2 suspensions of sulfadiazine produced higher concentrations of all forms of the drug in urine than did the tablets, there was the possibility that the suspensions might produce a sulfadiazine crystalluria. To investigate this, each sample of urine was centrifuged and an aliquot of the supernatant urine analyzed as before. The mean values obtained in the 3 groups, together with the standard

errors of the means, have been assembled in Table 4. By comparing the results given in Tables 3 and 4, it is obvious that there were no marked differences in the concentration of total, free or combined sulfadiazine in centrifuged *versus* uncentrifuged urine. The conclusion may be drawn that providing a sufficient volume

TOTAL URINARY OUTPUT OF SULFADIAZINE. To estimate the total mg. output of total, free and combined sulfadiazine at the various intervals collected, the concentration of the drug per ml. was multiplied by the number of ml. of urine collected and the means and standard errors have been assembled in Table 5. The

TABLE 3.—THE CONCENTRATION OF SULFADIAZINE IN MG. PER 100 ML. OF UNCENTRIFUGED URINE FOLLOWING ORAL ADMINISTRATION OF 4 GM. OF THE DRUG IN VARIOUS PHARMACEUTICAL FORMS

Pharmaceutical form	Concentration in urine: mean \pm standard error				
	0.5 hr.	1 hr.	2 hrs.	4 hrs.	6 hrs.
<i>Total Sulfadiazine</i>					
Tablets	17 \pm 0.21	84 \pm 1.4	314 \pm 4.0	112 \pm 9.2	182 \pm 16.5
Micronized powder	59 \pm 0.83	214 \pm 4.3	470 \pm 7.4	121 \pm 13.8	214 \pm 21.7
Microcrystals	87 \pm 1.40	301 \pm 4.9	692 \pm 9.5	135 \pm 11.2	176 \pm 13.6
<i>Free Sulfadiazine</i>					
Tablets	18 \pm 0.20	78 \pm 1.3	280 \pm 3.5	99.5 \pm 8.3	141 \pm 13.0
Micronized powder	58 \pm 0.84	188 \pm 3.2	394 \pm 5.8	97.5 \pm 13.0	167 \pm 14.7
Microcrystals	80 \pm 1.30	257 \pm 4.2	614 \pm 5.3	113 \pm 10.9	155 \pm 6.5
<i>Combined Sulfadiazine</i>					
Tablets	-0.1 \pm 0.07	0.6 \pm 0.26	3.4 \pm 0.95	12.5 \pm 2.3	41 \pm 4.8
Micronized powder	0.1 \pm 0.24	2.6 \pm 0.86	7.6 \pm 2.00	23.5 \pm 3.0	47 \pm 4.0
Microcrystals	0.7 \pm 0.16	4.4 \pm 0.87	7.8 \pm 2.20	22.0 \pm 2.7	21 \pm 3.2

TABLE 4.—THE CONCENTRATION OF SULFADIAZINE IN MG. PER 100 ML. OF CENTRIFUGED URINE FOLLOWING ORAL ADMINISTRATION OF 4 GM. OF THE DRUG IN VARIOUS PHARMACEUTICAL FORMS

Pharmaceutical form	Concentration in centrifuge urine: mean \pm standard error				
	0.5 hr.	1 hr.	2 hrs.	4 hrs.	6 hrs.
<i>Total Sulfadiazine</i>					
Tablets	19 \pm 0.35	73 \pm 2.0	31.6 \pm 5.9	110 \pm 12.7	178 \pm 21.2
Micronized powder	69 \pm 1.50	238 \pm 5.4	476 \pm 9.4	123 \pm 17.9	206 \pm 23.0
Microcrystals	99 \pm 2.00	242 \pm 5.8	697 \pm 17.9	140 \pm 18.0	192 \pm 17.8
<i>Free Sulfadiazine</i>					
Tablets	18 \pm 0.26	70 \pm 1.9	288 \pm 5.6	94 \pm 11.6	145 \pm 18.5
Micronized powder	73 \pm 1.40	214 \pm 5.0	485 \pm 8.0	107 \pm 18.4	170 \pm 20.1
Microcrystals	93 \pm 1.80	216 \pm 4.9	595 \pm 13.9	120 \pm 17.8	163 \pm 14.6
<i>Combined Sulfadiazine</i>					
Tablets	0.1 \pm 0.10	0.3 \pm 0.17	2.8 \pm 0.56	16 \pm 2.3	33 \pm 4.3
Micronized powder	-0.4 \pm 0.21	2.4 \pm 0.82	0.9 \pm 2.80	16 \pm 2.1	36 \pm 5.4
Microcrystals	0.6 \pm 0.60	2.6 \pm 0.88	10.2 \pm 1.90	20 \pm 2.5	29 \pm 5.7

of water is taken with the drug, there is no danger of sulfadiazine crystalluria from the 2 suspensions, even though the concentration of the drug in urine is a good deal higher than following use of the tablets. In view of the results obtained, however, it would be well to make certain that a large volume of water or other fluids be taken if one or other of the suspensions of sulfadiazine be used in therapy.

results indicate that those pharmaceutical preparations which were absorbed the more quickly into the blood stream, were also excreted in greater amount in urine, even up to 4 and 6 hours after administration. With a few exceptions, the difference between the mean total mg. outputs of the 3 pharmaceutical forms of sulfadiazine was of the order of 2.5 to 4 times

TABLE 5.—THE TOTAL MG. OUTPUT OF SULFADIAZINE IN URINE FOLLOWING ORAL ADMINISTRATION OF 4 GM. OF THE DRUG IN VARIOUS PHARMACEUTICAL FORMS

Pharmaceutical form	Mg output of sulfadiazine, mean \pm standard error				
	0 to 0.5 hr.	0.5 to 1 hr.	1 to 2 hrs	2 to 4 hrs.	4 to 6 hrs
<i>Total Sulfadiazine</i>					
Tablets	179 \pm 30	619 \pm 97	254 \pm 25	128 \pm 13	190 \pm 32
Micronized powder	440 \pm 51	1070 \pm 200	372 \pm 37	141 \pm 15	228 \pm 24
Microcrystals	640 \pm 52	1890 \pm 300	575 \pm 70	200 \pm 20	216 \pm 18
<i>Free Sulfadiazine</i>					
Tablets	196 \pm 29	602 \pm 91	232 \pm 12	115 \pm 12	153 \pm 17
Micronized powder	410 \pm 48	950 \pm 150	324 \pm 31	125 \pm 11	186 \pm 19
Microcrystals	540 \pm 63	1640 \pm 230	460 \pm 53	170 \pm 17	162 \pm 19
<i>Combined Sulfadiazine</i>					
Tablets	0.17	0.17	2.2	13	37
Micronized powder	0.3	1.2	4.8	16	42
Microcrystals	1.0	2.5	11.5	30	54

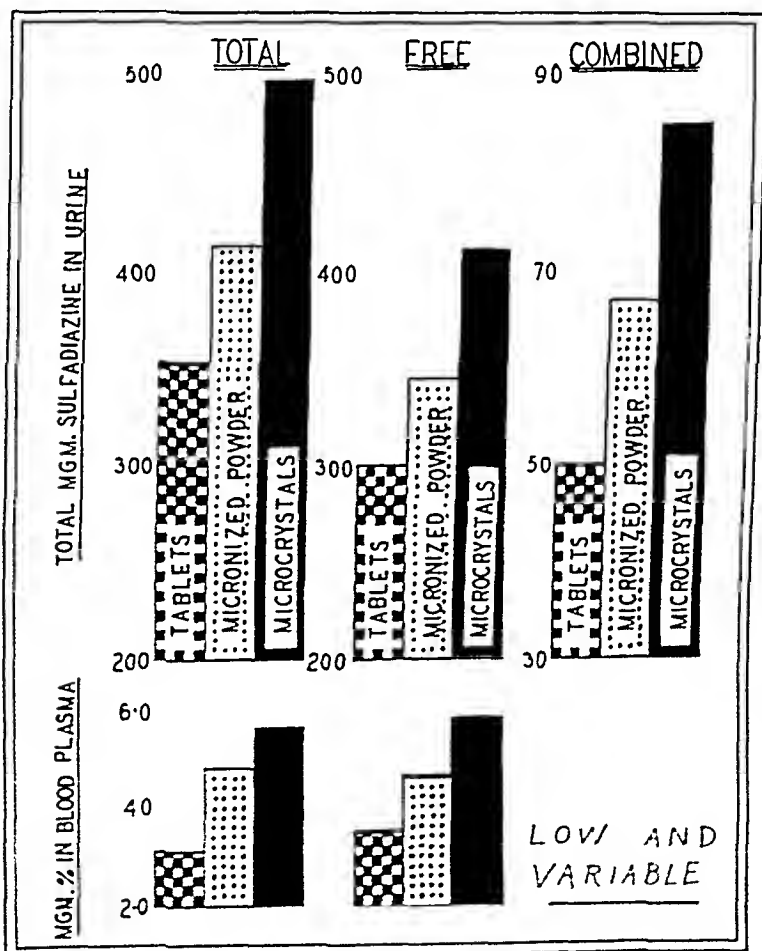


FIG. 1.—The 6-hour output of sulfadiazine in urine after administration of the drug in the form of tablets, a micronized powder suspension and as a suspension of microcrystals, compared with a representative example of the concentration in blood plasma.

the standard error of the mean difference at each interval.

The total mg. output in urine of total, free and combined sulfadiazine was calculated for the 6 hour period and for each pharmaceutical form in which the drug had been given. The results were averaged and these averages have been shown as a block diagram in Figure 1. To avoid a chart of confusing appearance, the standard errors of the means have not been indicated in Figure 1, but in the case of each form of the drug in urine, there was a significant difference between the 3 pharmaceutical forms of the drug. In order to show that the accumulated urinary output of sulfadiazine varied with the concentration in blood, except in the case of combined sulfadiazine, the concentration of the drug in blood plasma at the middle (2nd hour) interval was selected as representative of the blood levels and included in Figure 1. The data charted in Figure 1 summarize in a visual manner the main relationships found between blood and urine values and illustrate the quantitative differences in metabolism of the 3 types of sulfadiazine used in this study.

this preparation is used, there should be given plenty of fluids with or without alkali therapy as well.

The sediment of centrifuged specimens of urine was examined for crystals of free and combined sulfadiazine. In only a few instances were crystals found present, which was probably due to the fact that a considerable volume of water had been taken with the drug. Similarly there were little or no albuminuria, red blood cells, white blood cells nor casts found present in the urine.

REACTIONS TO SULFADIAZINE. During the course of this and of a following investigation, in which lactates were added to the suspension of microcrystals, sulfadiazine was given a total of between 150 and 200 times. A majority of the volunteers had had sulfadiazine therapy at least once before for some infection. It was expected, therefore, that there might have been some sensitization to the drug as occurs for example with sulfathiazole and a detailed clinical record was kept of each volunteer during and for a period up to almost a year in some cases after the experiment. In 1 volunteer, there was a slight urticarial rash the day after taking

TABLE 6.—THE EFFECT OF ORAL ADMINISTRATION OF 4 GM. OF SULFADIAZINE IN VARIOUS PHARMACEUTICAL FORMS UPON THE pH OF URINE

Pharmaceutical form	Mean pH of urine				
	0.5 hr.	1 hr.	2 hrs.	4 hrs.	6 hrs.
Tablets	5.9	5.9	5.8	5.7	5.8
Micronized powder . . .	5.5	5.8	5.6	5.6	5.7
Microcrystals	5.4	5.7	5.5	5.5	5.5

GENERAL EXAMINATION OF THE URINE. Since damage to the kidneys is a fairly common reaction to sulfadiazine therapy, a general examination was made upon each sample of urine. The pH of urine was determined with the aid of a Coleman pH electrometer and the mean values have been assembled in Table 6. The pH of urine was not markedly affected by administration of these drugs. Most values were slightly on the acid side of normal. The most acid pH values were found following the use of the suspension of microcrystals which again suggests that when

the drug but this rash did not appear again when the same person was given a second dose of sulfadiazine some 2 to 3 weeks later. Apart from this questionable reaction, there were no toxic effects noted in any of the volunteers.

Summary. Sulfadiazine was administered orally in 3 forms, (a) as tablets, (b) as a suspension of crushed or micronized powder and (c) as a suspension of microcrystals, in a dose of 4 gm. of the drug with 1 pint of water, to a total of 90 human volunteers, 30 given each preparation, with the following results: 1. As indicated

by estimation of whole blood and blood plasma sulfadiazine at intervals from 0.5 to 6 hours after administration, the drug was found most rapidly absorbed from the gut when given as microcrystals, next most rapidly as the micronized powder and least rapidly as the tablets.

2. Six hours after administration, the concentration of sulfadiazine in blood was almost the same no matter in which form it had been given.

3. The concentration of combined sulfadiazine in blood did not reach appreciable values until about 6 hours after administration, at which time the concentration was higher following the use of the micronized powder and microcrystals.

4. There was some indication that when sulfadiazine is given as the micronized powder or as microcrystals, it passes from plasma into the red blood cells to a rela-

tively less extent than when given as tablets.

5. The concentration of total, free and combined sulfadiazine in both centrifuged and uncentrifuged samples of urine collected at the same intervals as blood was withdrawn, was greatest following administration of the microcrystals, next following the micronized powder and least following the tablets. Values for the total output of sulfadiazine in urine roughly paralleled the blood values.

6. Little or no evidence was found of sulfadiazine crystalluria or of renal damage.

7. The urinary pH was on the acid side of normal, the most acid urine being obtained after use of the microcrystals.

8. Although many and probably most of the volunteers had had previous sulfadiazine therapy, there were no untoward or toxic reactions to the drug.

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THE EFFECT OF SODIUM AND POTASSIUM LACTATES UPON THE ABSORPTION AND ELIMINATION OF MICROCRYSTALLINE SULFADIAZINE*

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IN a previous communication,¹ it was shown that administration of a suspension of microcrystalline sulfadiazine possessed certain advantages over the use of tablets in that higher concentrations of the drug were obtained in blood and attained more quickly. At the same time, use of the suspension of microcrystals was followed by higher concentrations of the drug in urine, thus increasing the danger of sulfadiazine crystalluria and renal damage. To avoid these latter effects, a large fluid intake, preferably with alkali therapy as well, is indicated when these suspensions are employed therapeutically.

Sodium bicarbonate is the drug commonly employed to render the urine more alkaline during systemic sulfonamide therapy. However, there are several disadvantages in the use of sodium bicarbonate, especially if it is to be added to an aqueous preparation of sulfonamides, such as the suspension of microcrystalline sulfadiazine, and kept for some time before use. To affect appreciably the pH of urine, several grams of sodium bicarbonate must be taken by mouth. If dissolved in an aqueous preparation, such as the suspension of microcrystalline sulfadiazine referred to above, it slowly decomposes into the much more strongly alkaline sodium carbonate, with liberation of carbon dioxide, even at room temperature. The presence of alkaline sodium bicarbonates and carbonates would in time cause decomposition of various ingredients of the suspension of microcrystalline sulfadiazine previously

employed.¹ Sodium bicarbonate is soluble in water only to 10% or less, thus requiring a large volume dose of any sodium bicarbonate-sulfadiazine aqueous preparation. If an aqueous, pharmaceutical preparation of sulfadiazine happened to be, or to become, acid in reaction, carbon dioxide would be set free from any added sodium bicarbonate. These incompatibilities would render unstable and useless any combination of sodium bicarbonate and sulfadiazine in an aqueous pharmaceutical preparation meant to be kept for any length of time.

On the other hand, sodium lactate is readily soluble in water, forming a solution which is stable, about neutral in reaction and, when taken by mouth, it is converted into sodium bicarbonate in the body, so that the net pharmacologic effect is similar, after absorption, to that of giving sodium bicarbonate. We have therefore studied the effect on absorption and elimination in the body, of a suspension of microcrystalline sulfadiazine, similar in composition to that previously described, to which had been added 8.5 gm. of sodium lactate per 100 ml. of the suspension. The resulting preparation had a pleasant taste, the most pleasant of all of the suspensions of microcrystalline sulfadiazine studied in this and the previously reported investigation.¹

Ohnysty and Wolfson⁴ tried potassium bicarbonate in place of sodium bicarbonate, on the grounds that potassium bicarbonate is diuretic and does not promote

* This paper was presented in preliminary form at the annual meeting of the American Society for Pharmacology and Experimental Therapeutics, Atlantic City, March 1946.

retention of water in the extracellular body fluids as does sodium bicarbonate. They found potassium bicarbonate effective in preventing sulfonamide crystaluria. Therefore it was decided to compare sodium and potassium lactates and a further suspension of microcrystalline sulfadiazine, similar in composition to that previously described¹ but with the addition of 8.5 gm. of potassium lactate per 100 ml. of suspension, was investigated. The latter preparation was somewhat bitter and much less pleasant to the taste than was the preparation made with sodium lactate. These 2 preparations of lactates, together with the simple suspension of microcrystalline sulfadiazine, were made and placed at our disposal by the Pitman-Moore Company of Indianapolis, which company also provided us with a grant-in-aid of this research.

Technique. The suspensions of microcrystalline sulfadiazine with sodium and with potassium lactates were each given to 30 healthy, human volunteers, in a dose equivalent to 4 gm. of sulfadiazine, and the results compared with those previously reported for the microcrystalline suspension without the lactates.¹ Each volunteer voided his or her urine at 10 A.M. the day of the experiment and then took the respective suspension of the drug, together with a pint of water. At intervals of 0.5, 1, 2, 4 and 6 hours after administration, a sample of oxalated blood was obtained and the accumulated volume of urine collected, no urine having been voided and discarded between intervals. Determinations as described below and identical to those previously reported¹ were made, sulfadiazine being estimated by a slight modification of the method of Bratton and Marshall.² The results were statistically analyzed as in the previous communication,¹ using the formulae of Hill.³

BLOOD SULFADIAZINE. Means and their standard errors for the concentration of total, free and combined sulfadiazine in oxalated whole blood have been assembled in Table 1. The addition of lactates significantly accelerated the rate of absorption of sulfadiazine from the suspension of the microcrystals. In this respect,

sodium lactate was more effective than potassium lactate. The effect lasted until about the 4th hour after administration, after which there were no significant differences in the concentration of total and free sulfadiazine in whole blood. The concentration of combined sulfadiazine was low and variable and the values of so little significance that only means have been given in Table 1.

Differences in the concentration of sulfadiazine in blood plasma (Table 2) were of the same nature as those in whole blood, the lactates accelerating the absorption of microcrystalline sulfadiazine during the first 4 hours after administration. During the first 2 hours after administration, the average levels of total and free sulfadiazine in blood plasma were about 1.3 times those in whole blood, indicating a higher concentration in plasma than in the red blood cells. For all practical purposes, there were no differences in the distribution of sulfadiazine between plasma and red blood cells following the giving of the 3 pharmaceutical forms of the drug.

The differences in the rate of absorption of the 3 preparations of sulfadiazine were not due to differences in the pH of the suspensions. As measured in a Coleman pH electrometer and checked by color indicators, the pH of the suspension of microcrystals alone was 3.6, of the microcrystals plus potassium lactate 3.5 and of the microcrystals plus sodium lactate 5.0. From the evidence available, it was not possible to explain why lactates accelerate the rate of absorption of microcrystalline sulfadiazine. In conclusion, of the 3 pharmaceutical preparations of sulfadiazine studied in this and the previously reported investigation,¹ the preparation of microcrystals with sodium lactate proved to be the most efficacious in that it was pleasant to taste, most quickly absorbed from the gastro-intestinal tract, gave higher concentrations in whole blood and in blood plasma and, as will be described, was most quickly excreted in urine and made the urine least acid. These results, therefore, indicate that in sulfadiazine therapy, the

suspension of microcrystalline sulfadiazine with sodium lactate, as herein used, is the pharmaceutical preparation of choice, especially in the therapy of infants and in other instances where tablets are contra-indicated for one reason or another.

URINARY SULFADIAZINE. The concentrations of sulfadiazine in urine have been

TABLE 1.—THE CONCENTRATION OF SULFADIAZINE IN MG. PER 100 ML. OF WHOLE BLOOD FOLLOWING ORAL ADMINISTRATION OF 4 GM. OF THE DRUG IN VARIOUS

PHARMACEUTICAL FORMS

Pharmaceutical form	Concentration in whole blood: mean \pm standard error				
	0.5 hr.	1 hr.	2 hrs.	4 hrs.	6 hrs.
<i>Total Sulfadiazine</i>					
Microcrystals	1.3 \pm 0.09	2.7 \pm 0.14	4.5 \pm 0.22	7.1 \pm 0.41	7.1 \pm 0.41
" plus K lactate	1.7 \pm 0.13	2.9 \pm 0.27	4.8 \pm 0.22	6.8 \pm 0.26	6.4 \pm 0.28
" plus Na lactate	2.0 \pm 0.19	3.6 \pm 0.23	5.4 \pm 0.30	7.4 \pm 0.39	6.7 \pm 0.35
<i>Free Sulfadiazine</i>					
Microcrystals	1.3 \pm 0.08	2.6 \pm 0.14	4.3 \pm 0.16	6.9 \pm 0.32	6.4 \pm 0.53
" plus K lactate	1.8 \pm 0.13	3.1 \pm 0.19	4.8 \pm 0.22	6.8 \pm 0.25	6.1 \pm 0.24
" plus Na lactate	2.3 \pm 0.18	3.7 \pm 0.19	5.6 \pm 0.26	7.0 \pm 0.35	6.4 \pm 0.33
<i>Combining Sulfadiazine</i>					
Microcrystals	0.0	0.1	0.2	0.2	0.7
" plus K lactate	-0.1	-0.2	0.0	0.0	0.3
" plus Na lactate	-0.3	-0.1	-0.2	0.4	0.3

TABLE 2.—THE CONCENTRATION OF SULFADIAZINE IN MG. PER 100 ML. OF BLOOD PLASMA FOLLOWING ORAL ADMINISTRATION OF 4 GM. OF THE DRUG IN VARIOUS PHARMACEUTICAL FORMS

Pharmaceutical form	Concentration in blood plasma: mean \pm standard error				
	0.5 hr.	1 hr.	2 hrs.	4 hrs.	6 hrs.
<i>Total Sulfadiazine</i>					
Microcrystals	1.7 \pm 0.19	3.2 \pm 0.34	5.6 \pm 0.40	9.5 \pm 0.65	8.9 \pm 0.50
" plus K lactate	2.0 \pm 0.21	4.1 \pm 0.40	6.2 \pm 0.42	9.0 \pm 0.50	8.5 \pm 0.39
" plus Na lactate	2.7 \pm 0.36	5.2 \pm 0.34	7.7 \pm 0.51	10.3 \pm 0.47	9.1 \pm 0.56
<i>Free Sulfadiazine</i>					
Microcrystals	1.8 \pm 0.18	3.4 \pm 0.29	5.8 \pm 0.33	9.1 \pm 0.52	8.5 \pm 0.50
" plus K lactate	2.0 \pm 0.21	4.2 \pm 0.32	6.4 \pm 0.43	9.1 \pm 0.44	8.3 \pm 0.39
" plus Na lactate	2.9 \pm 0.29	4.9 \pm 0.31	7.5 \pm 0.42	9.9 \pm 0.58	8.4 \pm 0.49
<i>Combined Sulfadiazine</i>					
Microcrystals	-0.1	-0.2	-0.2	0.4	0.4
" K lactate	0.0	-0.1	-0.2	-0.1	0.2
" Na lactate	-0.2	0.3	0.2	0.4	0.7

TABLE 3.—THE CONCENTRATION OF SULFADIAZINE IN MG. PER 100 ML. OF UNCENTRIFUGED URINE FOLLOWING ORAL ADMINISTRATION OF 4 GM. OF THE DRUG IN VARIOUS PHARMACEUTICAL FORMS

Pharmaceutical form	Concentration in urine: mean \pm standard error				
	0.5 hr.	1 hr.	2 hrs.	4 hrs.	6 hrs.
<i>Total Sulfadiazine</i>					
Microcrystals	8.7 \pm 1.4	30.1 \pm 4.9	69.2 \pm 9.5	135 \pm 11.2	176 \pm 13.6
" plus K lactate	8.0 \pm 1.2	35.9 \pm 5.4	67.4 \pm 9.1	140 \pm 12.1	244 \pm 22.0
" plus Na lactate	9.7 \pm 4.5	48.8 \pm 13.8	105.0 \pm 10.2	190 \pm 18.0	232 \pm 20.5
<i>Free Sulfadiazine</i>					
Microcrystals	8.0 \pm 1.3	25.7 \pm 4.2	61.4 \pm 5.3	113 \pm 10.9	155 \pm 6.5
" plus K lactate	7.5 \pm 1.1	32.9 \pm 5.1	62.0 \pm 8.4	125 \pm 11.4	206 \pm 24.1
" plus Na lactate	8.9 \pm 1.2	42.4 \pm 5.3	95.5 \pm 9.0	164 \pm 15.8	217 \pm 18.5
<i>Combined Sulfadiazine</i>					
Microcrystals	0.7 \pm 0.16	4.4 \pm 0.87	7.8 \pm 2.2	22 \pm 2.7	21 \pm 3.2
" plus K lactate	0.5 \pm 0.14	7.0 \pm 0.52	5.4 \pm 1.0	15 \pm 2.6	38 \pm 3.4
" plus Na lactate	0.8 \pm 0.16	6.4 \pm 0.54	9.5 \pm 1.6	26 \pm 4.3	15 \pm 3.9

summarized in Table 3. While in general the mean levels of total and free sulfadiazine were higher when lactates were added to the administered microcrystals, the differences were not statistically significant until after about the 2nd hour, when the concentrations became a good deal higher after use of the preparations containing the lactates. The concentration of combined sulfadiazine varied considerably and it was not possible to state that lactates significantly affected the results.

values are given in Table 4. There was not much difference in the levels of total, free and combined sulfadiazine in centrifuged *versus* uncentrifuged urine, probably due to the large volume of water taken with the drugs and, as will be shown, to the relatively higher values for urinary pH when lactates were added to the microcrystalline suspension.

The total output of total and free sulfadiazine was, in most instances, appreciably and significantly higher following those

TABLE 4.—THE CONCENTRATION OF SULFADIAZINE IN MG. PER 100 ML. OF CENTRIFUGED URINE FOLLOWING ORAL ADMINISTRATION OF 4 GM. OF THE DRUG IN VARIOUS PHARMACEUTICAL FORMS

Pharmaceutical form	Concentration in centrifuged urine: mean \pm standard error				
	0.5 hr.	1 hr.	2 hrs.	4 hrs.	6 hrs.
<i>Total Sulfadiazine</i>					
Microcrystals	9.9 \pm 2.0	24.2 \pm 5.8	69.7 \pm 17.9	140 \pm 18.0	192 \pm 17.8
" plus K lactate	10.0 \pm 1.2	35.2 \pm 7.9	75.5 \pm 12.4	142 \pm 19.0	238 \pm 23.4
" plus Na lactate	9.4 \pm 1.9	37.5 \pm 8.5	97.4 \pm 11.0	207 \pm 33.7	290 \pm 35.6
<i>Free Sulfadiazine</i>					
Microcrystals	9.3 \pm 1.8	21.6 \pm 4.9	59.5 \pm 13.9	120 \pm 17.8	163 \pm 14.6
" plus K lactate	9.8 \pm 2.1	30.8 \pm 6.9	66.1 \pm 12.9	123 \pm 17.7	201 \pm 24.1
" plus Na lactate	9.4 \pm 1.5	36.7 \pm 7.2	86.2 \pm 10.6	187 \pm 26.5	246 \pm 34.8
<i>Combined Sulfadiazine</i>					
Microcrystals	0.6 \pm 0.60	2.6 \pm 0.88	10.2 \pm 1.9	20 \pm 2.5	29 \pm 5.7
" plus K lactate	0.2 \pm 0.19	4.4 \pm 1.4	9.4 \pm 1.6	19 \pm 4.5	47 \pm 5.3
" plus Na lactate	0.0 \pm 0.28	0.8 \pm 0.62	11.2 \pm 1.6	20 \pm 9.0	44 \pm 7.0

TABLE 5.—THE TOTAL MG. OUTPUT OF SULFADIAZINE IN URINE FOLLOWING ORAL ADMINISTRATION OF 4 GM. OF THE DRUG IN VARIOUS PHARMACEUTICAL FORMS

Pharmaceutical form	Mg. output of sulfadiazine in urine: mean \pm standard error					
	0-0.5 hr.	0.5-1 hr.	1-2 hrs.	2-4 hrs.	4-6 hrs.	0-6 hrs.
<i>Total Sulfadiazine</i>						
Microcrystals	6.4 \pm 0.52	18.9 \pm 3.0	57.5 \pm 7.0	200 \pm 20.2	216 \pm 18.8	496 \pm 43.3
" plus K lactate	7.3 \pm 1.5	23.7 \pm 2.7	70.9 \pm 6.9	224 \pm 16.5	263 \pm 18.2	580 \pm 35.8
" plus Na lactate	5.5 \pm 1.0	26.2 \pm 3.3	70.5 \pm 5.2	228 \pm 15.1	251 \pm 20.2	576 \pm 36.6
<i>Free Sulfadiazine</i>						
Microcrystals	5.4 \pm 0.63	16.4 \pm 2.3	46.0 \pm 5.3	170 \pm 17.6	162 \pm 19.8	411 \pm 47.6
" plus K lactate	6.8 \pm 1.0	21.8 \pm 2.6	66.2 \pm 6.3	199 \pm 14.8	225 \pm 18.8	506 \pm 36.0
" plus Na lactate	7.9 \pm 1.0	25.3 \pm 2.7	63.8 \pm 4.5	206 \pm 15.3	229 \pm 17.2	520 \pm 36.1
<i>Combined Sulfadiazine</i>						
Microcrystals	1.0	2.5	11.5	30	54	85
" plus K lactate	0.5	1.9	4.7	25	35	74
" plus Na lactate	0.6	0.9	6.7	22	25	56

In view of the relatively high concentrations of sulfadiazine in urine, there was the possibility of a sulfadiazine crystalluria and hence estimations were made of the concentrations of the several forms of the sulfonamide upon the supernatant urine of centrifuged specimens. These

suspensions of microcrystals containing lactates (Table 5). On the other hand, there were no significant differences in the total output of combined sulfadiazine. In the last column to the right of Table 5, has been given a summation figure for the output of sulfadiazine in urine over the

period of 6 hours of the experiment, and, from the values given in this column, the same general conclusion may be drawn as was with the total outputs at the shorter intervals.

General Examination of Urine and Toxic Reactions. The addition of lactates to the suspension of microcrystalline sulfadiazine made the urine definitely less acid, as may be seen from the mean values for urinary pH assembled in Table 6. Of the 2 lac-

Summary. 1. Sodium and potassium lactates were separately added to a suspension of microcrystalline sulfadiazine and each preparation was given orally in a dose of 4 gm. of sulfadiazine to 30 human volunteers.

2. The lactates accelerated the absorption of sulfadiazine microcrystals from the gastro-intestinal tract and gave higher initial concentrations of the drug in whole blood and in blood plasma.

TABLE 6.—THE EFFECT OF ORAL ADMINISTRATION OF 4 GM. OF SULFADIAZINE IN VARIOUS PHARMACEUTICAL FORMS UPON THE pH OF URINE

Pharmaceutical form	Mean pH of urine				
	0.5 hr.	1 hr.	2 hrs.	4 hrs.	6 hrs.
Microcrystals	5.4	5.7	5.5	5.5	5.5
" plus K lactate . . .	5.5	5.7	6.0	6.0	6.1
" plus Na lactate . . .	5.5	6.1	6.2	6.3	6.3

tates, sodium lactate was the more effective in making the urine less acid. In all of these volunteers, only 1 or 2 instances of transient albuminuria were seen, and the sediment from the centrifuged specimens of urine showed little evidence of sulfadiazine crystalluria. There was little or no evidence of renal damage as indicated by the absence or near absence of red blood cells, white blood cells and casts in the urinary sediment. There were no untoward or toxic clinical reactions.

3. Lactates also accelerated the output of total and free sulfadiazine in urine and increased the urinary pH. There was no evidence of renal damage nor of other untoward clinical reactions.

4. In all these respects, the preparation of microcrystals with sodium lactate was more effective than the preparation made with potassium lactate and in addition the preparation made with sodium lactate had a much more pleasant taste.

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HYPOTHERMIA AND ELEVATED SERUM MAGNESIUM IN A PATIENT WITH FACIAL HEMANGIOMA EXTENDING INTO THE HYPOTHALAMUS

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THE association of facial and intracranial hemangiomas has been observed fairly often—82 cases having been reported up to 1936 (Greenwald and Koota¹³)—but extension of a facial hemangioma into the intracranial cavity is indeed rare. An infant, in whom a facial hemangioma entered the intracranial cavity by way of the internal auditory canal, is the subject of the present paper. Such an extension of the tumor alone would make the case noteworthy, but the further spread of the tumor to the hypothalamus and the development of hypothermia and an increase in the concentration of serum magnesium are points of even greater interest. Hypothermia, associated with tumor of the hypothalamus has been observed (Ratner,²³ Cushing,⁸ Obregia, Dimoleseo and Constantinesco,²¹ Foerster,¹⁰ and Davison and Selby⁹), but an increase in the concentration of serum magnesium in such circumstances has, to our knowledge, not been previously reported.

Case Report. The patient, a white female infant, was born on April 6, 1939. Jaundice, present at birth, persisted for about 3 weeks. When the infant was 10 days old, a small pink papule was observed on her left cheek. The papule rapidly enlarged, assuming a purplish-red color, and by the time the infant was 12 weeks old, had spread over the upper left cheek, the left ear and postauricular area, and the left side of the scalp. It bled readily when rubbed, or otherwise traumatized. Irradiation of the area failed to check the growth. During the 12th week of life a thrush infection of the nose and pharynx developed and the infant had difficulty in swallowing and breathing. Occasionally she was apneic for as long as 30 seconds.

On June 29 the infant, then 12 weeks old, was admitted to the hospital of the University of Pennsylvania, on the service of Dr. J. C. Gittings. Her rectal temperature was 98.5° F. The hemangiomatous lesion on the left side of the face and head was widespread (Fig. 1). Examination of the



FIG. 1.—Photograph showing the extent of the hemangioma.

eyes revealed nothing of significance except a persistent pupillary membrane on the right; the fundi showed no vascular abnormalities. Laryngoscopic examination disclosed a small, flat, soft purplish-red mass in the left piriform sinus and pharynx which was most prominent near the opening of the Eustachian tube. Roentgenograms of the skull revealed no evidence of intracranial calcification or demineralization of the calvarium. A small area of increased density in the right upper lung, which was ascribed to atelectasis, was the only abnormality observed in roentgenograms of the chest.

Examinations of the blood yielded the following values: hemoglobin, 10 to 8.4 gm. per 100 ml.; erythrocytes, 3.8×10^6 per c.mm.; leukocytes, 6 to 21 thousand per c.mm. (35% neutrophils, 54% lymphocytes, 11% monocytes). Urinalysis on several occasions was negative except for traces of albumin and occasional hyaline casts. Serologic tests (Kolmer and Kahn) were negative.

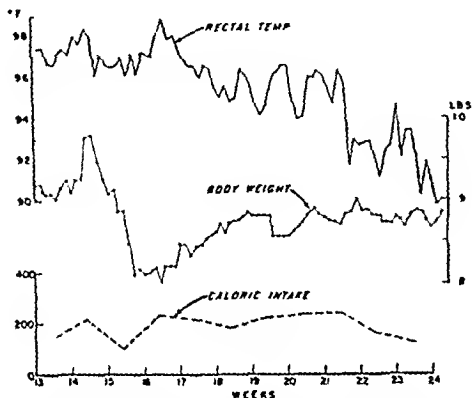


FIG. 2.—Rectal temperature, body weight and caloric intake during stay in hospital.

The essential clinical features during the last 11 weeks of life are illustrated in Figure 2. The rectal temperature was subnormal practically throughout the entire period of observation. During the last 4 weeks of life, the temperature ranged between 94° and 90° F., and on 2 occasions when a low registering thermometer was employed it was 88° and 89° F. On admission to hospital the infant's weight was 9 pounds, 3 ounces. During the 14th and 15th weeks of life diuresis developed and her weight decreased from 9.8 to 8.1 pounds. Following this drop there was a gradual increase in weight, the level at the time of death being 8.9 pounds. The infant's caloric intake was subnormal throughout the period of observation, the daily average being 189 calories (Fig. 2), which is about one-third of the estimated daily caloric requirement for a normal infant of the same age and weight. Although no estimation of the metabolic rate was obtained, it is evident that metabolism must have been very low, since after the 16th week the infant's weight increased even though the caloric intake was only a fraction of the normal requirement.

The results of analyses of the serum electrolytes are shown in Table 1. The serum was obtained from blood removed by cardiac

puncture and collected under paraffin oil at the time of death. Since comparable normal values of magnesium and calcium were desired, analyses were made of the blood serum of 4 normal infants from 2 to 4 months of age. The results of these measurements are given in Table 2. When compared with the established normal values, the concentration of serum magnesium in our patient was increased 67%; serum calcium, on the other hand, was decreased 28%. Serum total base and chloride also were less than normal.²⁴ Serum inorganic phosphorus was increased 95% above Stearns and Warweg's²⁵ value for infants 2 to 4 months of age. The slight increase in BHCO_3 is in accord with the experimental data of Stadie, Austin and Robinson²⁶ which indicated an inverse change in bicarbonate of 1 mM per liter for every 4° to 5° F. change in body temperature at either constant CO_2 tension or constant pH.

Throughout the period of observation in the hospital, the infant was in a state of lethargy. She could be aroused sufficiently to take food but when her appetite was satisfied she soon lapsed into a semisomnolent state. Crying was rare. During the last few weeks of life a peculiar lardy, gelatinous appearance was evident. There was no visible edema. Death occurred on Sept. 17, 1939, in the 24th week after admission to hospital.

AUTOPSY (12 hours after death). *Gross Observations.* An enormous vascular tumor covered the greater part of the left side of the face, the entire left ear, the left temporo-occipital region of the scalp and the adjoining part of the neck. The growth, which was somewhat elevated above the surface of the skin, reached to the outer canthus of the eye but did not invade the eyelids. In the region of the ear it extended into, and partially occluded, the external auditory meatus. Reflection of the calvarium and dura revealed no abnormalities of the leptomeninges. On removal of the brain a moderately friable, somewhat lobulated, grayish-pink mass of tissue was found in the left cerebellopontile angle, where it was firmly adherent to the leptomeninges and indented the tonsil of the cerebellum and inferior portion of the pons. Laterally the mass was attached to the adjacent dura. It also filled the internal auditory canal and the middle ear, and was coextensive with the mass in the external auditory meatus.

In addition, a small portion of the tumor was found at the base of the brain, where it encompassed the hypophysial stalk and was firmly adherent to the tuber cinereum. Section of the brain revealed abundant tumor tissue within the fourth ventricle, continuous with that in the cerebellopontile angle. The entire ventricular system was moderately dilated.

The thoracic and abdominal viscera appeared normal except for patchy consolidation of the lungs.

and each lobule was surrounded by a zone of dense collagenous tissue of varying width. Within the fourth ventricle, most of the lobules were covered with a single row of cuboidal cells resembling ependyma (Figs. 3, A, and 4, B). The entire intracranial portion of the tumor was regarded as a malignant hemangio-endothelioma.

The mass in the left cerebellopontile angle surrounded and invaded the acoustic (Fig. 3, B) and adjacent cranial nerves to a variable degree, causing moderate degenerative

TABLE 1.—SERUM ELECTROLYTES IN INFANT WITH HYPOTHERMIA

Components	Values	Deviation from normal
Total base	138 mEq per L.	Decrease
Calcium	4.1 mEq per L.	Decrease
Magnesium	3 mEq per L.	Increase
Chloride	93.7 mEq per L.	Decrease
Total CO ₂	66 vol. %	Increase
BHCO ₃	28.1 mEq per L.	Increase
Inorganic P	12.3 mg. per 100 ml.	Increase
BPr*	10.2 mEq per L.	Decrease

* BPr = 0.97 (Pr) (pH—5.26) where Pr = gm. protein per 100 ml. Serum protein = 4.9 gm. per 100 ml. and pH is assumed 7.4.

TABLE 2.—SERUM ANALYSES IN 4 NORMAL INFANTS, AGED 2 TO 4 MONTHS

Subject	Calcium (mEq per L.)	Magnesium (mEq per L.)
Web	5.9	1.98
McL	5.8	2.02
Bern	5.8	2.05
Nel	6.0	2.12

Methods. The brain stem was removed *en masse* and divided into 3 blocks. Each was embedded in paraffin, serially sectioned at 8 microns, and every tenth section stained with hematoxylin and eosin. The diencephalon and adjoining midbrain were sectioned in the horizontal plane, and the remainder of the brain stem transversely.

Microscopic Findings. The tumor in the scalp consisted of myriad well-formed capillary channels supported by fibroblastic tissue. The lumens of the channels were lined by a single layer of flat and evenly distributed endothelial cells. No mitotic figures were observed. Histologically, the picture was that of a benign hemangioma. In the intracranial part of the tumor (Fig. 3) the capillary channels were relatively less numerous, the main bulk of the tissue being composed of spindle-shaped cells of indefinite outline, with homogeneous cytoplasm and irregularly elongated, finely chromatic nuclei. There were moderate numbers of mitotic figures. The tumor was lobulated,

changes as manifested by proliferation of the endoneurium and the sheath cells of Schwann. The tumor in the cerebellopontile angle was continuous through the foramen of Luschka with that in the fourth ventricle, and a part of the tumor had broken through the tela choroidea and proliferated extraventricularly (Fig. 4). Examination of serial sections revealed that the intraventricular portion of the tumor extended from the midpontine region to the level of the decussation of the pyramids. The tumor had distended the fourth ventricle but had not invaded or visibly damaged the cerebellum, pons, or medulla oblongata, except for the ponticulus of the left side (Fig. 3, A), which was partially disintegrated. The tufts of the choroid plexus were displaced by the tumor but otherwise appeared normal. The area postrema showed no visible abnormalities. A small portion of the tumor had reached the right cerebellopontile angle (Fig. 4). No tumor tissue was observed in the region of



FIG. 3.—Intracranial portions of the tumor. In *A*, from the region of the fourth ventricle, tumor masses are attached to the inferior and superior aspects of the roof of the fourth ventricle respectively. The tissue surrounding the fourth ventricle has a normal appearance except at the lateral angle of the ventricle where the base of the ponticulus is partially disintegrated. $\times 90$. (AIP Neg. 95106.) In *B*, from the region of the cerebellopontine angle, the tumor surrounds and partially invades the acoustic nerve. $\times 30$. (AIP Neg. 95102.)



FIG. 4.—The medulla oblongata at the mid-olivary level. The main portion of the tumor is in the region of the left cerebellopontine angle, left foramen of Luschka, above the ventricular roof, and within the fourth ventricle. Bits of tumor evidently escaped from the right foramen of Luschka into the adjacent cerebellopontine angle. The tumor is decidedly nodular. The nerve in the lower left part of the photograph is probably the vagus or glossopharyngeal. $\times 10$. (AIP Neg. 95095.)

the midbrain, nor was there any other abnormality aside from slight dilatation of the aqueduct.

Serial sectioning of the base of the brain was done in the horizontal plane, as mentioned previously. In the lowest section available, *i. e.*, at the level of the more inferior part of the optic chiasm and at the

anterior wall of the stalk exhibited a mild proliferation of glia and a homogeneity of the perivascular glial sleeves. The encompassing pars tuberalis appeared normal. At a somewhat higher level (Fig. 5, *B*), the tumor had invaded and destroyed much of the retro-infundibular portion of the ventromedial nucleus. The uppermost extension

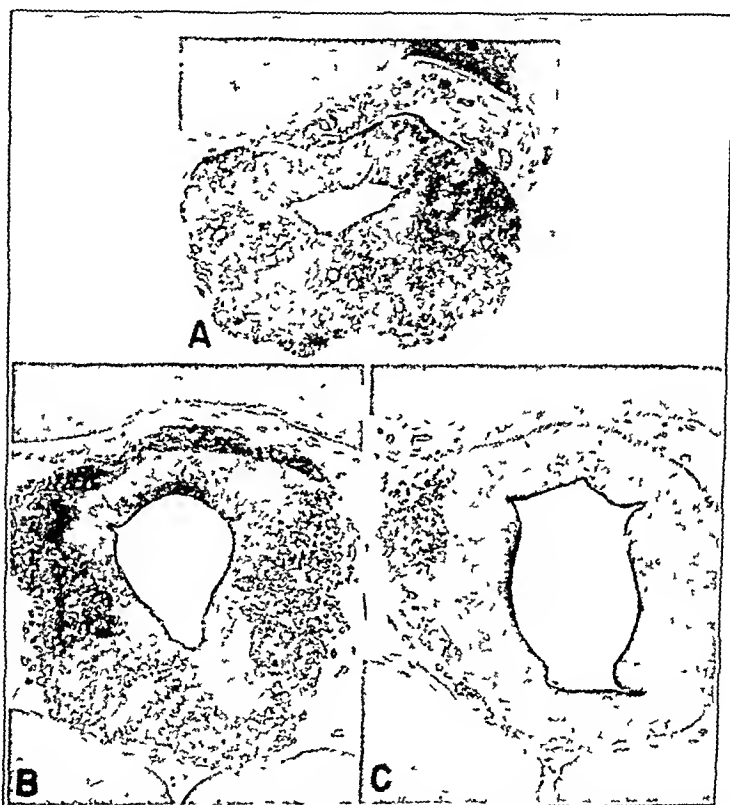


FIG. 5.—Horizontal sections through the base of the brain at the levels of (A) the lower aspect of the optic chiasma, (B) the mid-portion of the chiasma and the lower third of the mammillary bodies, and (C) the upper portion of the chiasma and the mid-region of the mammillary bodies. In A the tumor has destroyed the posterior and lateral walls of the infundibular stalk, the posterior part of the median eminence and the lowermost portion of the ventromedial hypothalamic nucleus. The infundibular recess of the third ventricle is visible $\times 30$ (AIP Neg. 95099). In B, the ventromedial nucleus of both sides is virtually destroyed (AIP Neg. 95107). In C, the highest level at which the tumor grew, only the most lateral portion of the ventromedial nucleus is invaded $\times 30$ (AIP Neg. 95097). At none of the levels are the optic chiasm (above) or the mammillary bodies (below) affected by the tumor.

junctional zone between the neurohypophysis and the tuber cinereum (Fig. 5, A), the tumor had invaded and almost completely replaced the posterior and lateral walls of the uppermost portion of the hypophysial stalk as well as the median eminence and the adjacent retro-infundibular part of the ventromedial hypothalamic nucleus. The

of the tumor was at the level of the more superior part of the optic chiasm and the middle of the mammillary bodies (Fig. 5, C). Here the tumor was restricted to one side of the tuber cinereum, the ventromedial nucleus of which it had superficially invaded. A study of sections at higher levels disclosed degenerative changes in the paraventricular

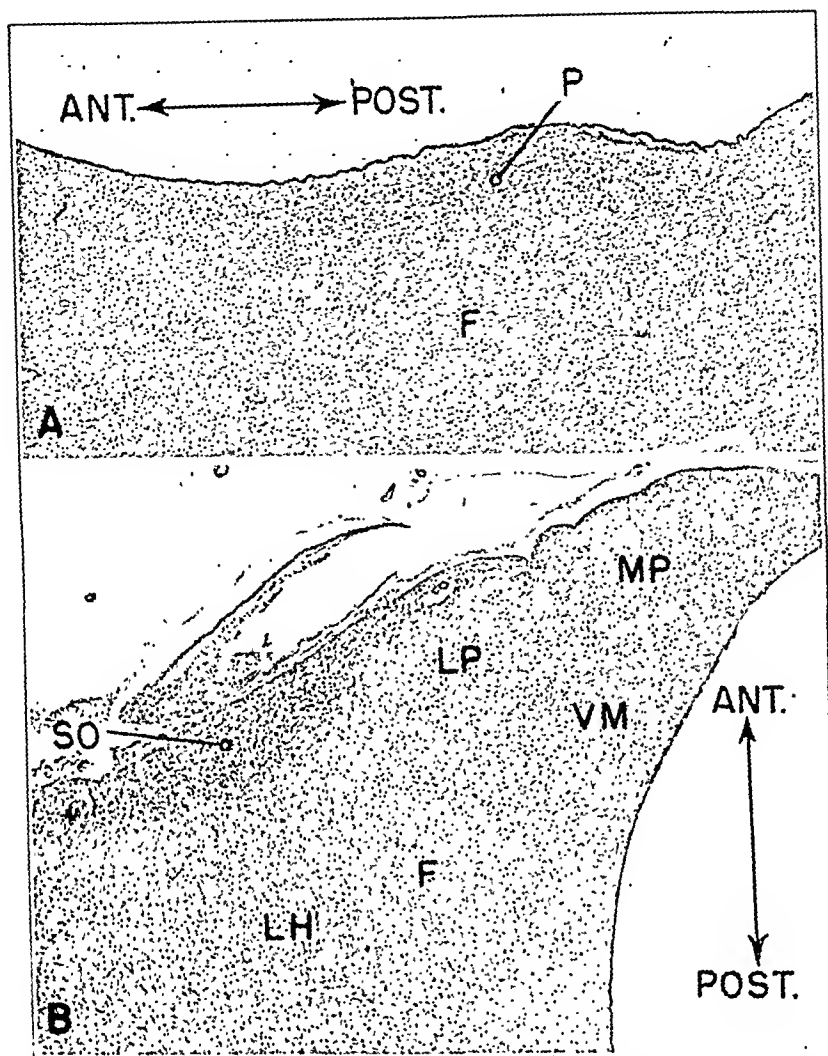


FIG. 6.—A, Horizontal section of the hypothalamus at the level of the mid-portion of the paraventricular nucleus (P). There is a moderate depopulation of the larger cells composing this nucleus. The third ventricle is dilated. The fornix (F) shows no change. $\times 30$. (AIP Neg. 95101.) B, Dorsolateral part of the supraoptic nucleus (SO) shows a slight loss of ganglion cells. (At lower levels the ventromedial part of the supraoptic nucleus showed a greater reduction in cells.) No changes are visible in the ventromedial (VM), medial preoptic (MP), or lateral preoptic (LP) nuclei, or in the lateral hypothalamic area (LH) or the fornix (F). The third ventricle is dilated. $\times 30$. (AIP Neg. 95098.) The arrows are included for purposes of orientation.

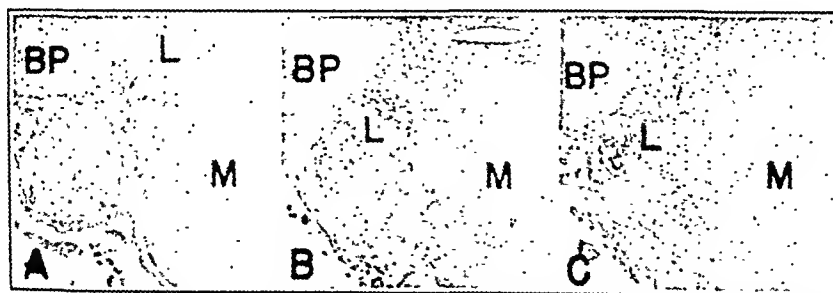


FIG. 7.—Caudal region of the hypothalamus (horizontal sections), showing a tumor nodule at 3 levels of the more inferior part of the mamillary body. In A the tumor is lateral to the mamillary body (M) and beneath the lateral hypothalamic area (L) and the medial aspect of the basis pedunculi (BP). In B it is adherent to, and invades superficially the lateral hypothalamic area, while in C it occupies a small circumscribed portion of the lateral hypothalamic area. In B and C a minor portion of the tuberomamillary nucleus has been replaced by the tumor. (AIP Negs. 95512-95514.)

and supraoptic nuclei, moderate in the former (Fig. 6, A) and slight in the latter (Fig. 6, B).

Another tumor nodule was found in the region of the posterior part of the hypothalamus (Fig. 7). It was small, had proliferated in the meninges just lateral to the mamillary body, and had invaded the more inferior part of the lateral hypothalamic area. Only a moderate number of cells of the tuberomamillary nucleus had been destroyed. The lateral mamillary nucleus and the nucleus intercalatus were unaffected.

Study of the other nuclei of the hypothalamus, including the preoptic, suprachiasmatic and lateral tuberal, revealed no abnormalities. The optic chiasma was free from change. The remainder of the brain also was normal. The pituitary gland was not available for study. Of the other endocrine glands, only the adrenal and pancreas were sectioned. Neither showed abnormalities. Sections from the lungs disclosed acute lobular pneumonia.

Discussion. The pathway by which the tumor had entered the intracranial cavity was apparent. It had spread through the external auditory meatus, middle ear, Eustachian tube, and obviously had penetrated the labyrinth, for it had reached the internal auditory canal and entered the intracranial cavity along the course of the acoustic nerve. Proliferating in the region of the left cerebellopontile angle, it had traversed the adjacent foramen of Luschka, then gained the fourth ventricle, from which a part of the tumor escaped to the region of the right cerebellopontile angle; in addition, fragments of the tumor had presumably been carried by the current of the cerebrospinal fluid to the base of the brain where they took root in the hypophyseal stalk and adjacent tuber cinereum as well as in the caudolateral part of the hypothalamus.

In attempting to provide an anatomic basis for the hypothermia and the decrease in metabolism, only 2 regions come into consideration: the lower brain stem and the base of the hypothalamus together with the neurohypophysis. In regard to the lower brain stem, it is well recognized in experimental animals that hypothal-

amic fibers concerned with temperature regulation descend diffusely in the tegmental region of the midbrain, pons and medulla oblongata (Magoun,²⁰ Keller,¹⁸ Beaton, Leininger and McKinley²), and the evidence indicates that the same is true in man (List and Peet¹⁹). Since in our case the pons and medulla oblongata were apparently unaffected by the tumor, except for the ponticulus which seems to be nothing more than a support for the attachment of the choroid plexus, it may be assumed that fibers concerned with temperature regulation were not compromised in their passage through this part of the brain stem. Especial attention was paid to the area postrema owing to the possibility that it might have been damaged by the tumor, but no defect in this structure was observed.

It is necessary also to consider the possibility that the damage to the hypophyseal stalk and median eminence may have given rise to the hypothermia and the reduction of metabolic activity. The lesion had destroyed the posterior wall and part of the lateral walls of the hypophyseal stalk as well as the retro-infundibular portion of the median eminence. In experimental animals such as the rat, neither hypothermia nor a significant decrease in the rate of basal metabolism occurs after section of the hypophyseal stalk (Anderson¹). A persistent increase of 0.5° to 1° C. in body temperature was observed in dogs in which the hypophyseal stalk had been sectioned, temperature regulation being otherwise unaffected (Hemingway, Rasmussen, Rasmussen and Wikoff¹⁶), but it is quite possible that during operation the adjacent anterior hypothalamic region was injured. Following hypophysectomy, the basal metabolic rate is reduced, and the body temperature may show a tendency to fall, but there is never the degree of hypothermia which was observed in our case. In 34 hypophysectomized dogs studied by Solari²⁵ the body temperature was within the normal range in 31; the remaining 3 had a mild degree of hypothermia, which was ascribed to damage incurred by the

tuber cinereum at the time of operation. In 2 other dogs in which the tuber cinereum was cauterized after hypophysectomy, the body temperature fell markedly, in 1 instance reaching 90.5° F. From these considerations it appears highly unlikely that the lesion responsible for the hypothermia in our case was in the neurohypophysis. Unfortunately the adenohypophysis was not available for study.

The hypothalamus was the only other structure affected, and here the damage was restricted to the more inferior part of the ventromedial nucleus bilaterally and to a very small portion of the caudal part of the tuberomammillary nucleus unilaterally. There was no morphologic evidence of injury to cells beyond the regions of tumor infiltration. Obviously the heat maintenance mechanism was functionally inadequate. It is conceded that this mechanism is situated in the more caudolateral part of the hypothalamus and that the mechanism for heat dissipation is predominantly anterior in location, *i. e.*, chiefly in the preoptic and supraoptic regions of the hypothalamus (Ranson,²² and others). The ventromedial nucleus occupies a position midway between these 2 mechanisms, and forms the bulk of the more medial part of the tuber cinereum. That experimentally induced lesions of the tuber cinereum lead to hypothermia has long been known (Isenschmid and Schmützler¹⁷) but usually such lesions involved both the medial and lateral portions of the hypothalamus. Blair and Keller³ have been able to eliminate the thermogenic mechanism by destroying the gray matter of the caudolateral hypothalamus but the effective lesions always damaged parts of the tuber cinereum as well. The lateral part of the tuber cinereum has been regarded as of importance in temperature regulation by Clark, Magoun and Ranson,⁶ but not the ventromedial nucleus, since body temperature remained virtually unaltered when it was bilaterally destroyed. Stoll,²³ on the other hand, adduced evidence that the medial hypothalamic region does play an impor-

tant rôle in temperature regulation, but he could not limit such activity to any one nucleus. Our case would seem to provide compelling evidence that *the ventromedial nucleus is an essential part of the heat maintenance mechanism*. It is doubted that the small unilateral lesion in the tuberomammillary nucleus was contributory to the development of hypothermia since small hypothalamic lesions generally do not give rise to symptoms unless they are bilateral.

It was striking in our case that the metabolic level was lowered to such a degree that the body weight was maintained on a caloric intake considerably less than normally required. Experimentally induced lesions of the hypothalamus also have been shown to cause a fall in basal metabolic rate (Grafe and Grünthal,¹² Grünthal, Mulholland and Strieck,¹⁴ Strieck, Grünthal and Urra,³⁰ Bloch^{4,5}). Thus, in well-controlled experiments on cats in which the tuberal and adjacent regions were damaged bilaterally, and the pituitary body spared, Bloch⁵ observed that the fall in basal metabolic rate was usually relatively greater than the fall in body temperature, and that oxygen consumption was sometimes decreased as much as 20 to 25% in the presence of a normal body temperature. From these observations Bloch concluded that though the hypothalamic mechanisms of temperature regulation and basal metabolism overlap anatomically they show a certain degree of independence functionally.

Owing to a similarity in our patient's behavior to that of an animal in hibernation, especial interest was attached to the 67% increase in serum magnesium. The increase in serum magnesium resembles that seen in certain species during hibernation, Suomalainen,³¹ for instance, having observed a 70% increase in serum magnesium in the hibernating hedgehog. In hibernation the essential features are general torpidity, loss of temperature control, and quiescence of the sympathico-adrenal system as reflected by a decrease in adrenalin content of the adrenals, and

hypoglycemia (Suomalainen³²). Efforts have been made to determine the factor or factors responsible for the increment of magnesium in the blood serum in hibernating as well as non-hibernating animals. Steadman, Ariel and Warren,²⁷ testing the effect of hypothermia on serum magnesium, found in rabbits in which the body temperature had been rapidly lowered to levels between 55.4° and 71.6° F., that the average increase in serum magnesium was 24%; they ascribed the increase in serum magnesium either to a cessation of kidney function, which may have prevented the excretion of magnesium, or to the cold state, which may have prevented its return to its storage sites, mainly the bones and muscles. Notwithstanding the lethargic pseudohibernation produced in these animals, it is well recognized that neither lowered temperature nor other environmental factor is a *sine qua non* for the development of true hibernation (Gorer¹¹). Cleghorn,⁷ for instance, has observed that marmots of the lower Adirondacks normally go into seclusion in September when the weather is warm and the food plentiful.

In viewing the various phenomena which go to make up the state of hibernation, one is struck most by the torpor. This condition is akin to sleep, for as Gorer¹¹ has remarked, "Anybody who has dealt with hibernating mammals must know that an animal so lethargic as to appear lifeless may be awakened if manipulated at all carelessly." The site in the central nervous system responsible for the rhythmicity with which sleep follows wakefulness is generally conceded to be the caudal hypothalamus and adjoining rostral midbrain. It seems logical to assume that the same may apply to hibernation, the essential difference between sleep and hibernation being in rhythmic-

ity. It should be pointed out that man is capable of a certain degree of hibernation if Volkov's³³ report is true that peasants in the region of Pskov, Russia, spend most of the winter asleep before a fire, awaking only once a day to tend the fire and to eat a little bread. In our patient, whom we regard as having been in a state of pseudohibernation, the essential lesion was hypothalamic. One small unilateral lesion was in the region responsible for the maintenance of the sleep-waking rhythm, while the bulk of the lesion was but a short distance away. Whether the hypothalamus can be held responsible for shifts in magnesium, in order to modify the *milieu interne* and protect against an unfavorable environment, is a point still to be determined.

Summary. In a case of hemangioma of the face which developed into a malignant hemangio-endothelioma and spread rapidly into the intracranial cavity, where it proliferated in the region of the cerebello-pontile angle, fourth ventricle, and base of the third ventricle, there were persistent hypothermia, lowered metabolism, and increased concentration of serum magnesium—findings resembling those in normal animals during hibernation. The tumor had invaded and partially destroyed the posterior and lateral walls of the hypophysial stalk, the posterior half of the median eminence and the more inferior part of the ventromedial hypothalamic nucleus bilaterally, and a small area of the tuberomammillary nucleus unilaterally.

Conclusion. The symptoms in this case are to be ascribed to damage of the ventromedial nucleus and consequent interruption of fibers which descend the brain stem as part of the autonomic nervous system.

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CLINICAL STUDIES OF THE PHARMACOLOGIC EFFECTS OF TETRAETHYL AMMONIUM CHLORIDE IN HYPERTENSIVE PERSONS MADE IN AN ATTEMPT TO SELECT PATIENTS SUITABLE FOR LUMBODORSAL SYMPATHECTOMY AND GANGLIONECTOMY

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SOME patients with early essential hypertension and an occasional patient with malignant hypertension are improved dramatically by lumbodorsal sympathectomy and ganglionectomy. A reliable method for selecting those patients with arterial hypertension who are suitable for extensive sympathectomy has not yet been found. Of the wide variety of tests now under examination, none has more accurately predicted a good result than has the careful grading of the severity of the vascular disease (Page and Corcoran⁷). Those with minimal vascular disease and those with necrotizing arteriolitis seem most favorably influenced by operation.

The barbituric acid hypnotics do not primarily affect the sympathetic ganglia or the vasomotor nerves. It is therefore not surprising that, although they have received wide usage, tests employing hypnotics such as sodium amytal have been signally unsuccessful as methods of selecting candidates for operation.

The inadequacy of the present methods of selection has led to the continued search for one which would reproduce the results of sympathectomy by administration of a drug. Acheson and Moe¹ and Acheson and Pereira² reported that the tetrathyl ammonium ion depressed the function of the sympathetic ganglia in cats. Ing⁴ and Ing and Wright⁵ reported that of all the sodium salts tetraethyl ammonium ions had the least curariform activity. Lyons⁶ made preliminary studies to ascer-

tain whether tetraethyl ammonium bromide duplicated the results of sympathectomy in man, and would therefore be useful in patient selection. Their initial results were encouraging.

In this report of the effect of the tetraethyl ammonium ion on 16 hypertensive patients studied on the medical service of the Research Division of the Cleveland Clinic, the commercial bromide was converted into the chloride to avoid the sedative effect of bromide ions. Eleven of the patients had essential hypertension, 4 malignant hypertension and 1 chronic glomerulonephritis. Dr. W. James Gardner, Chief of the Neurosurgical Department, performed the Smithwick type of lumbodorsal sympathectomy on 12 of them.

METHOD OF STUDY. Tetraethyl ammonium chloride solutions containing 100 to 150 mg. per cc. of saline were used after sterilization by Seitz filtration. Dosages which averaged 33 mg. (range 25 to 51) per kg. of body weight were given to the first 8 patients by intravenous infusion. However, the undesirable reactions were so alarming that in the next 8 patients doses of from 4 to 7 mg. per kg. of body weight were used. These were given by single intravenous injections.

The experiments were conducted as part of the studies made before hypertensive patients are subjected to operation. For comparative purposes, the results ob-

tained with the widely employed "sedation tests" are included.

All measurements of blood pressure were made in the supine position. Control values represent the average of measurements made twice daily during at least 7 days rest in bed and serve as a reference point for all results reported.

33 mg. per kg. The change in blood pressure began within 1 minute after injection and was maximal in 3 to 5 minutes. It was sustained for 10 to 15 minutes after which time it gradually returned to pre-injection levels (Chart 1).

The nature of the hypertension, its duration, etiology and severity bore no

TABLE 1.—RESULTS OF INTRAVENOUS INJECTION OF TETRAETHYL AMMONIUM CHLORIDE

No.	Control blood pressure (mm. Hg)	Control pulse rate	Dosage (mg./kg.)	Post-injection arterial blood pressure	Pulse rate	Fall in systolic pressure	Fall in diastolic pressure	Change in pulse
1 . . .	150/100	80	51	140/100	80	10	0	0
2 . . .	176/110	78	40	110/80	72	66	30	-6
3 . . .	260/150	120	31	230/140	140	30	10	+20
4 . . .	185/130	88	30	180/130	88	5	0	0
5 . . .	183/124	88	28	115/80	96	68	44	+8
6 . . .	220/134	84	28	145/80	80	75	54	-4
7 . . .	240/140	90	28	190/130	96	50	10	+6
8 . . .	200/130	80	25	125/70	88	75	60	+8
9 . . .	230/145	100	7	150/115	120	80	30	+20
10 . . .	180/110	80	6	110/70	120	70	40	+40
11 . . .	240/140	120	6	148/110	96	92	30	-14
12 . . .	200/130	100	4	190/140	100	10	+10*	0
13 . . .	190/120	140	4	140/90	120	50	30	-20
14 . . .	160/120	100	4	140/110	120	20	10	+20
15 . . .	220/140	100	4	200/150	120	20	+10*	+20
16 . . .	170/115	80	4	100/75	112	70	40	+32
Mean . . .	200/128	96	18.8	151/104	103	49	24	+8

* + indicates blood pressure levels above control values.

Results. (a) EFFECT OF ADMINISTRATION OF TETRAETHYL AMMONIUM CHLORIDE ON ARTERIAL PRESSURE AND PULSE RATE. Of the 16 patients who received intravenous injections of tetraethyl ammonium chloride, 14 exhibited significant reduction of blood pressure (Table 1). Nine of them showed a marked fall of blood pressure. In 7 of these 9, normal levels were observed within 5 minutes after injection. Five showed only a moderate drop of blood pressure (10 to 80 mm. Hg systolic and 10 to 54 mm. Hg diastolic). The mean change in pressure was 49 mm. Hg systolic and 24 mm. Hg diastolic. The magnitude of reduction of arterial pressure was not directly related to the size of dose. In 8 cases an average dose of 4.9 mg. per kg. of body weight produced a mean reduction in blood pressure of 52 mm. Hg systolic and 40 mm. Hg diastolic, compared with a mean fall of 47 mm. Hg systolic and 28 mm. Hg diastolic following an average dosage of

apparent relationship to the degree of fall in blood pressure, as shown by the fact that 1 subject with malignant hypertension and 1 with chronic glomerulonephritis had normal blood pressure levels after the injection of 28 mg. of tetraethyl ammonium chloride per kg. of body weight.

No constant effect on the pulse rate was observed. One subject experienced tachycardia which increased the pulse rate by 40 beats per minute, but psychogenic factors undoubtedly contributed. Three patients had no change in pulse rate, and 4 had slight slowing of pulse rate. In 8 there was an average increase of 17 beats per minute.

(b) OTHER EFFECTS OF TETRAETHYL AMMONIUM CHLORIDE (TABLE 2 AND CHART 2). A wide variety of pharmacologic effects was observed (Table 2). They increased in number and intensity with increasing amounts of the drug. The first phase of the reaction was characterized by mydriasis, ptosis of the lid and

numbness and tingling. Mydriasis was a constant finding in all 16 patients, and was associated with complete cycloplegia with doses greater than 10 mg. per kg. of body weight. The pupils responded readily to pilocarpine, but slowly to physostigmine whose action depends upon intact parasympathetic ganglia and the consequent liberation of acetylcholine. Some degree

of ptosis of the lids was observed in 14 patients. It appeared early and was often extreme. It was not associated with enophthalmos, suggesting that paralysis of the levator palpebri superioris had occurred. Numbness and tingling immediately after injection was noted by 14 patients. Although most marked in the extremities, they were also experi-

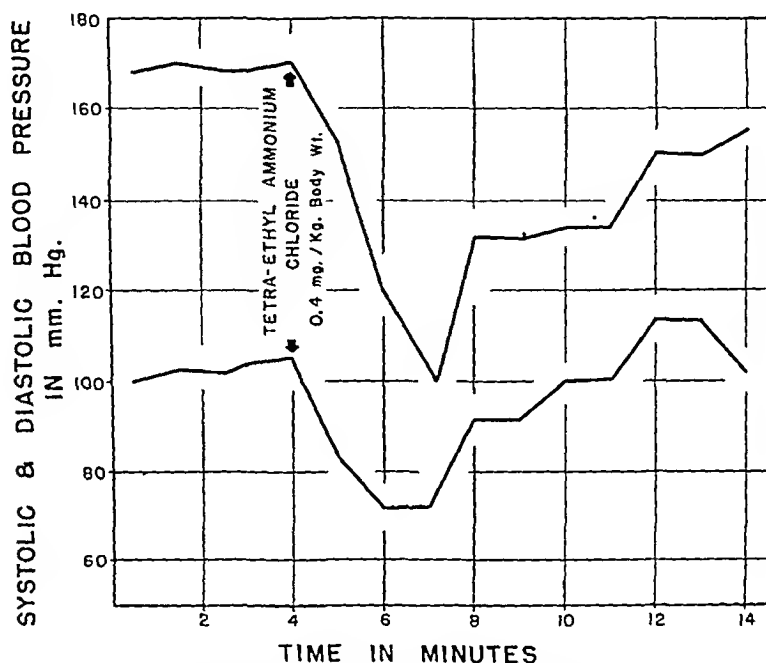


CHART 1.—Effect on the arterial blood pressure of the intravenous injection of tetraethyl ammonium chloride (0.4 mg. per kg. body weight).

TABLE 3.—EFFECTS OF INTRAVENOUS INJECTION OF TETRAETHYL AMMONIUM CHLORIDE, SODIUM AMYTAL SEDATION AND LUMBODORSAL SYMPATHECTOMY AND GANGLIONECTOMY ON ARTERIAL BLOOD PRESSURE

Patient	Control blood pressure (mm. Hg)	Blood pressure					
		Following intravenous injection of tetraethyl ammonium chloride (mm. Hg)		Following sodium amytal sedation		Two weeks after lumbodorsal sympathectomy and ganglionectomy	
		Lowest level	Degree of reduction	Lowest level	Degree of reduction	Average	Degree of reduction
1	150/100	140/100	10/0	120/70	30/30	120/84	30/16
2	176/110	110/80	66/30	156/100	20/10	140/90	36/20
4	183/130	180/130	3/0	150/110	33/20	180/130	5/0
6	220/134	145/80	75/54	154/100	66/34	220/134	0/0
8	200/130	125/70	75/60	180/116	20/14	200/126	0/4
9	230/145	150/115	80/30	140/100	90/45	210/130	20/15
10	180/110	110/70	70/40	130/90	50/20	194/118	+14/+8*
12	200/130	190/140	10/+10*	180/130	20/0	190/124	10/6
13	190/120	140/90	50/30	160/100	30/20	200/120	+10/0*
14	160/120	140/110	20/10	135/100	25/20	168/110	+8/10*
15	220/140	200/150	20/+10*	192/105	28/35	220/120	0/20
16	170/115	100/75	70/40	146/100	24/15	160/115	10/0
Average	190/124	144/101	46/23	154/102	35/22	184/117	7/7

* + indicates blood pressure levels above control values.

enced in the tongue, where they were associated with an unpleasant metallic taste.

The second stage of the drug's activity, represented by dryness of the mouth and generalized muscular weakness, occurred in about half of the patients. Objectively the musculature was atonic and voluntary motion required much effort. The patients complained of lassitude and weakness. Nasal congestion was noted by 5 of them. It was apparently due to sympatholytic activity of the drug, since similar phenomena appear after bilateral stellate ganglionectomy.³

to complete inability to speak because of muscular weakness. Rest temporarily restored control but after a few words spoken with obvious effort, the patient was again inarticulate. Dysphagia had a similar progressive course, until the patient was completely unable to swallow. Concomitantly, respiration became difficult because of relaxation of the neck and throat muscles. In 1 patient respirations depended entirely upon diaphragmatic activity because of complete intercostal paralysis.

Following injection of 40 mg. per kg., 1 patient progressed rapidly through the

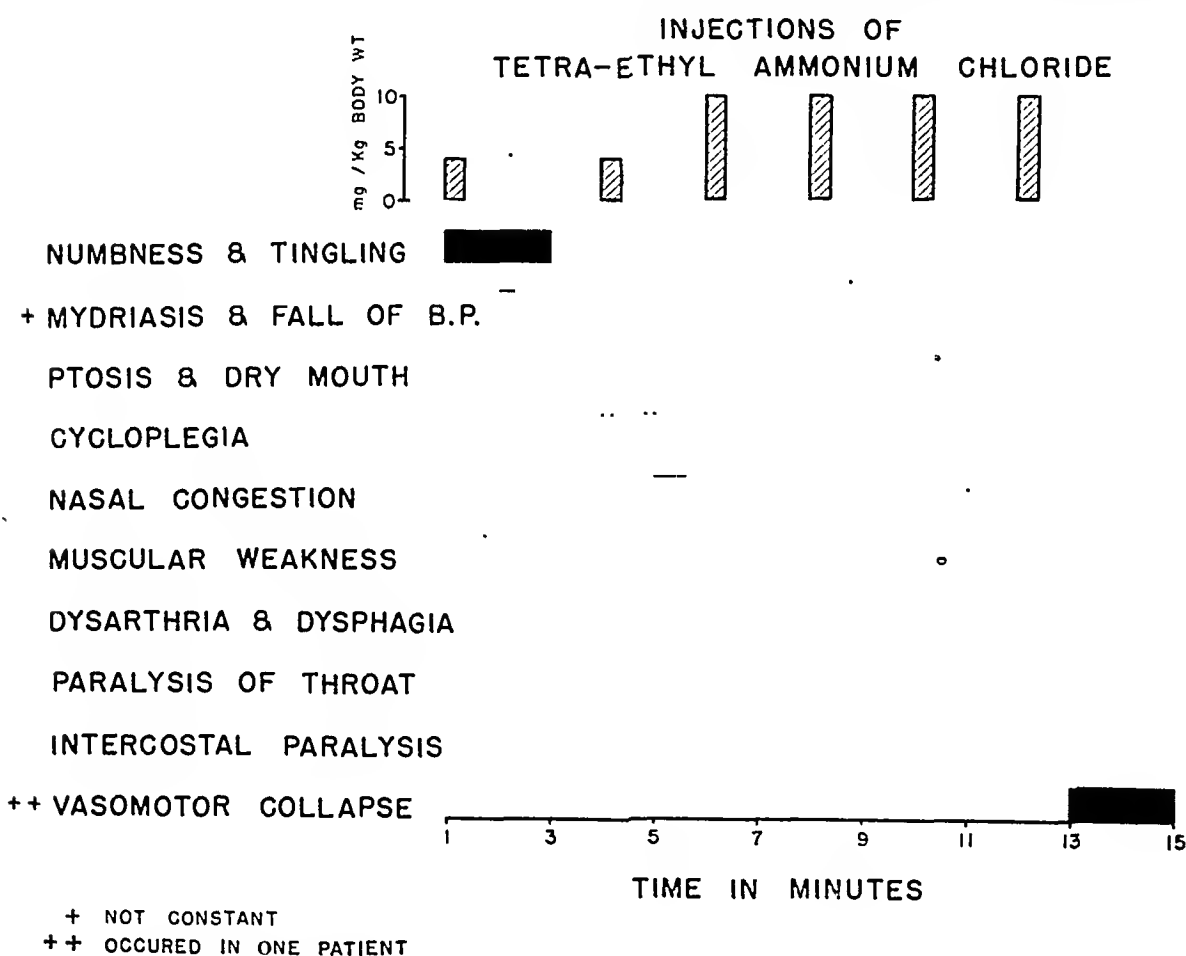


CHART 2.—Illustration of the pharmacologic effects of tetraethyl ammonium chloride.

The third stage was experienced only by those patients who received intravenous infusions of large amounts of tetraethyl ammonium chloride. The manifestations seemed to be primarily curariform. Dysarthria appeared first. Speech was initially slow and studied; later it progressed

above phases and developed complete circulatory collapse. He became cyanotic, lost consciousness and blood pressure and pulse were imperceptible. Voluntary respiration ceased. Artificial respiration, positive pressure oxygen administration, and intravenous injection of 2 mg. of

prostigmine were necessary to save life. After 5 hours he seemed to have recovered, except that the blood pressure did not return to its previous hypertensive level until the next day. Three additional patients required intravenous injections of 1 mg. of prostigmine for the control of alarming toxic symptoms. Rhonchi were heard by auscultation in 2 patients. One developed a severe asthmatic attack which was relieved by intravenous administration of 0.5 gm. of aminophylline.

Chart 2 illustrates the approximate time of appearance and duration of symptoms and signs which develop after repeated injections of tetraethyl ammonium chloride.

(c) COMPARISON OF EFFECTS OF TETRAETHYL AMMONIUM CHLORIDE, SODIUM AMYTAL SEDATION AND LUMBODORSAL SYMPATHECTOMY ON ARTERIAL PRESSURE IN HYPERTENSIVE PATIENTS. Twelve of the 16 patients were subjected to lumbodorsal sympathectomy. The blood pressure of each had been affected favorably by both tetraethyl ammonium chloride and sodium amytal sedation before operation (Table 3). The average fall in arterial pressure induced by each of these agents was 46 mm. Hg systolic and 23 mm. Hg diastolic and 35 mm. Hg systolic and 22 mm. Hg diastolic respectively. Two to 4 weeks after operation only 2 of these 12 patients had blood pressure levels measured at rest in the supine position that were lower than preoperative readings.

Discussion. If tetracthyl ammonium chloride had a highly selective depressing action on sympathetic ganglia, it should be possible to estimate pharmacologically the effect on blood pressure of lumbodorsal sympathectomy and ganglionectomy. This would provide a method for selecting candidates suitable for operation. However, the results presented indicate that in addition to its effect on the sympathetic ganglia it affects the parasympathetic ganglia, sensory nerve fibers and impairs

motor function. Mydriasis and dry mouth represent inhibition of the parasympathetic components. All of our patients experienced some degree of numbness and tingling immediately following injection of the drug, suggesting that it acts upon sensory nerve fibers as well. Its curariform activity was indicated by dysarthria, dysphagia, ptosis and, finally, intercostal and diaphragmatic paresis.

A drug which acts so diffusely in human beings might be expected to affect the blood pressure in a manner different from that of sympathectomy and ganglionectomy. That this is true is indicated by the fact that the degree of arterial pressure reduction induced by tetraethyl ammonium chloride bears no relationship to that following sympathectomy.

Summary. Eleven patients with essential hypertension, 4 with malignant hypertension and 1 with chronic Bright's disease were given intravenous injections of varying amounts of tetraethyl ammonium chloride to determine whether the reduction of blood pressure induced by this drug had any relationship to the effect of lumbodorsal sympathectomy on arterial pressure. Fourteen of the 16 patients had appreciable reduction of blood pressure after tetraethyl ammonium chloride as well as after the sodium amytal test. Twelve of these were operated upon, but only 2 of them had any significant change in resting supine blood pressure measurements 2 to 4 weeks after operation.

The pharmacologic effects of tetraethyl ammonium chloride can be attributed to relative depression of the autonomic nervous system, stimulation of the peripheral sensory nerves and curariform action. The effects of the drug increased in number and in severity with the size of the dose. Fall of arterial pressure, mydriasis, peripheral numbness and tingling and ptosis of the lids appeared first. During the next stage the mouth became dry and muscular weakness and nasal congestion

appeared. Finally, curariform effects became pronounced and led to dysarthria, dysphagia and intercostal paralysis. One patient developed vasomotor collapse, unconsciousness and apnea, but recovered after treatment.

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THE ROLE OF TRAUMA AS A POSSIBLE ETIOLOGIC FACTOR IN REGIONAL ENTERITIS

THE EFFECT OF NON-PENETRATING TRAUMA ON THE SMALL INTESTINE OF DOGS

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AND

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THE etiologic importance of trauma in regional enteritis is a controversial subject. Most authorities are inclined to discount its importance.^{3,9}

One of the cases seen by us, recently, aroused our interest in this subject.¹² A young soldier developed a regional enteritis confined to the proximal jejunum several months after a non-penetrating injury to the abdomen had been received in a motorcycle accident. A few other cases have been reported in the literature, in which there is a precedent history of trauma, and its etiologic importance is implied.^{2,7,8,10} These cases are very rare, however, and no proof exists that the trauma was the causative agent. In discussions of trauma to the abdomen, in general, little emphasis is placed on non-penetrating trauma, unaccompanied by intestinal perforation or severe hemorrhage.^{4,5,6,11,13} Experimental studies dealing with this subject are likewise scarce. Among these should be mentioned the negative report by Bell,¹ who found that interference with the blood supply of the intestinal tract does not result in a cicatrizing enteritis. Reichert and Mathes¹⁰, however, succeeded in producing cicatrizing lesions of the small bowel by obstructing the mesenteric lymphatics with sclerosing agents.

We were interested in determining what effect crushing trauma, short of perforation, would have on the small intestine. The dog was chosen as the experimental animal, chiefly because of its size. This feature simplified the experimental prob-

lems. We were, of course, aware of the great resistance to infections of the dog's peritoneum, as compared with that of a human being.

Experimental Procedure. Adult mongrel dogs were used, varying in size between 7.5 and 23.0 kgms. The dogs were anesthetized with intravenous nembutal. They were not fasted the day of the operation. It was felt that the presence of rough food particles and a changed intestinal flora during digestion and absorption may enhance the effect of the trauma. The peritoneum was entered through a median or perimedial incision. A 10 cm. (approximately) segment of the jejunum and ileum was isolated and traumatized.

The trauma was produced by a special corrugated steel clamp. The screws were tightened as tightly as possible, and immediately released. This was done in order to simulate the momentary trauma usually involved in the production of abdominal injuries. The injured intestinal segments were immediately replaced in the peritoneal cavity, and the animal returned to the cage, after closure of the abdominal wall. Food was not withheld.

The animals were observed for appetite, vomiting, and the character of the stool, especially with regard to consistency, and presence or absence of blood.

Most of the animals were sacrificed 3 to 7 months after exposure to the trauma. During the early part of the experiment, abdominal exploration in the anesthetized animal was attempted, but this procedure was abandoned because it yielded insufficient information.

On autopsy, the gross appearance of the

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bowel and mesentery were noted, and sections were taken of the bowel and regional lymph nodes for microscopic examination.

Results. Immediate Results of Trauma: As was pointed out above, the clamp was applied momentarily, and in the process, about 8 to 10 cm. of ileum and jejunum were crushed. Upon removal of the clamp, the central portion of the compressed bowel was pale and ischemic. The anti-mesenteric side showed numerous hematomas. At various points on the anti-mesenteric side, the serosa and muscularis were split, with a resultant herniation of the mucosa. Hematomas were produced on the mesenteric side and in the adjacent mesentery as well, but the intestinal wall usually remained intact at this point (Fig. 1).

bowel by fibrous and omental adhesions (Fig. 2). The omentum and vascular adhesions appeared to attach themselves to the injured bowel, especially on the anti-mesenteric side. These adhesions matted together the injured segments, attaching them to other parts of the bowel, the abdominal wall, and solid viscera. In spite of the presence of very sharp angulations, there was no evidence of serious interference with bowel lumen. Small areas of apparent thickening of bowel wall, chiefly due to invagination, were noted, but concentric hypertrophy with significant interference with the calibre of the lumen was not seen.

The regional lymph nodes were enlarged. This was more marked in the ileo-cecal mesentery. In the living anesthetized

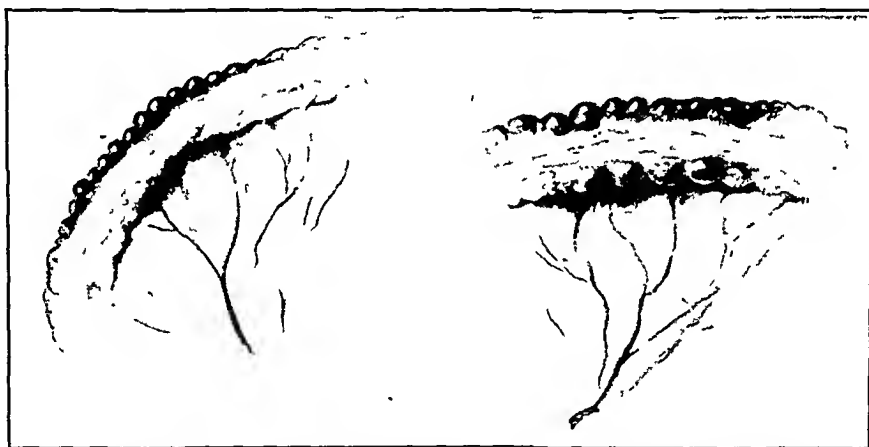


Fig. 1.—Appearance of bowel immediately after crushing injury. Note the splitting of the muscularis with herniation of mucosa and hematoma formation.

General Condition of the Animals: The animals commenced eating well shortly after surgery. Although some loss of weight did occur in most animals, this was not great (1–2 kgms.). All the animals retained their interest in food. No vomiting was noted.

The bowel movements were generally unchanged. But on several occasions, loose stools were noted, and a few times, gross blood was seen in the stools.

Gross Appearance: The most conspicuous gross finding was the distortion of the

animal, these adhesions, and hypertrophied lymph nodes, formed an extremely vascular granuloma-like mass, which bled profusely when disturbed.

The intestinal mucosa appeared intact grossly, with one exception—where a small shallow depression was seen, which appeared to be a superficial mucosal ulcer.

Microscopic Appearance: The mucosa itself was not involved. The glands were intact, and no true ulcerations were observed. In the submucosa, an abnormal accumulation of round cells was encount-

ered. This cellular exudate consisted chiefly of lymphocytes, some polymorphonuclear leucocytes, and an occasional eosinophile. No giant cells were seen (Fig. 3). The lymph follicles seemed larger and more abundant than normal, and the accumulation of lymphocytes seemed to spread beyond the boundary of the follicle.

The submucosa seemed thickened occa-

sionally. In some animals, much fibrous tissue was seen on the submucosa, and this fibrosis seemed to spread into the muscularis. The injured area appeared to heal by fibrous tissue replacement and in one dog (Fig. 4), the muscularis was replaced by fibrous tissue running in different directions in an irregular manner.

In other instances, complete disruption of muscularis resulted in no fibrous tissue



FIG. 2.—Gross appearance of the bowel several months after injury. Adhesions and kinking of bowel are marked.



FIG. 3.—Accumulation of round cells in submucosa, and muscularis mucosae. $\times 50$.

replacement, and the mucosa and submucosa were lying adjacent to the serosa. In this case (Fig. 5), no muscularis was seen in certain segments of the bowel.

The most conspicuous change seen in the serosa consisted of newly formed capillaries and round cell infiltration consistent with newly formed granulation tissues



FIG. 4.—Fibrous tissue replacement of muscularis and fibrosis of submucosa. $\times 50$.

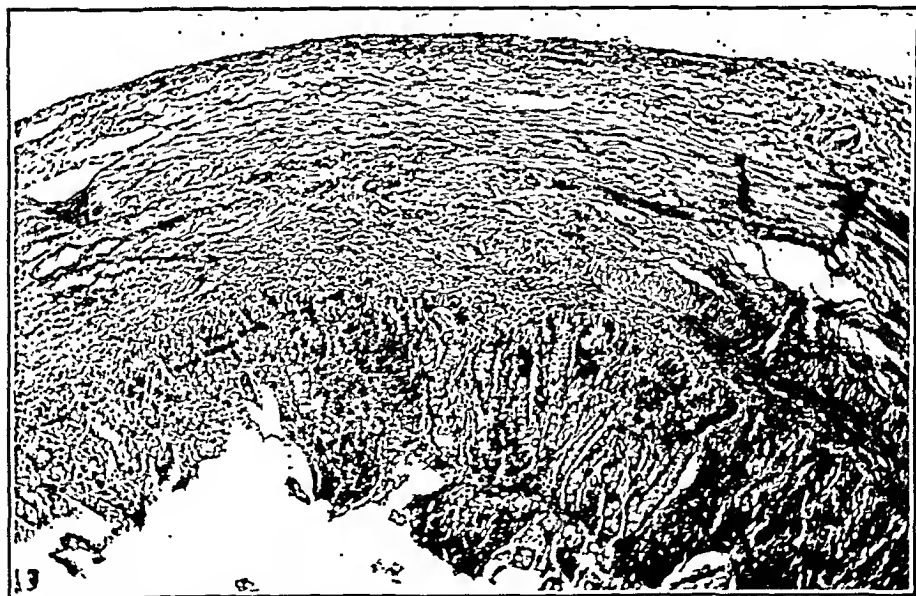


FIG. 5.—Complete absence of muscularis. The mucosa rests on serosa. $\times 100$.

(Fig. 6). Infrequently, a foreign tissue reaction was seen in the serosa, and in such areas, an occasional giant cell was seen.

Discussion. In human beings, abdominal trauma, which is not productive of severe hemorrhage or immediate perforation of a hollow viscus, is not looked upon as a serious lesion. The immediate post-traumatic period is observed with anxiety, but when this period passes uneventfully, later complications are rarely thought of. When abdominal symptoms recur after several months, the preceding trauma is apt to be overlooked as a factor of importance.

that the intake of food may have been limited by abdominal pain.

While the lesions seen did not simulate, either grossly or microscopically, those seen in regional enteritis, yet some features compatible with a chronic inflammation were present. Among these features may be mentioned the round cell infiltration, the fibrous tissue proliferation, and the new capillary formation seen in the serosa. The dissimilarity of this histologic lesion in the experimental animal from regional enteritis does not preclude the possibility that the healing process after trauma, in



FIG. 6.—Newly formed capillaries and round cell infiltration in the serosa. $\times 100$.

We succeeded in traumatizing severely the dogs' small intestines without producing gross perforation or severe hemorrhage.

The immediate post-traumatic course was relatively uneventful. Later in the course of the healing of this trauma, there were no conspicuous objective signs, although it is possible that some subjective symptoms, such as pain, may have been experienced by the animals. The fact that all of them lost some weight suggests

the human being, might produce changes similar to those seen in regional enteritis.

One thing seems obvious—that in the process of healing of non-penetrating and non-perforating intestinal trauma, long-lasting or permanent deformity of the bowel architecture may occur. Symptoms may not be produced till long after the injury, because as the healing process advances, more interference with the bowel lumen and motility may occur.

The fibrous tissue replacement of injured muscle fibers, or the accumulation of granulation tissue, may conceivably result in interference of motility and reduction of the bowel lumen. That this fibrosis in the muscularis and submucosa, seen in some of our animals, did not result in a narrowing of the bowel lumen and eventual stenosis is not unusual, when we remember that this injury did not involve equally the entire circumference of the bowel, but just one segment at a given level. It is conceivable, however, that with an appropriate combination of circumstances, a stenosis could be produced after many weeks or months; that is, after the fibrous tissue has had a chance to contract.

In spite of the fact that no obstruction or severe interference with the small bowel motility resulted from this injury, it is felt that, even in the dog, significant alteration in small bowel functioning was produced.

The authors gratefully acknowledge the assistance given by Miss Rita K. Tortmase, R. N., in carrying out the surgical procedures.

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And in human beings undergoing trauma of similar severity, the end results may be more serious, if the healing process is accompanied by more fibrosis and lymphoid tissue hyperplasia.

Summary and Conclusions: 1. Segments of ileum and jejunum were traumatized by crushing with a blunt instrument.

2. The animals survived the initial injury without ill effect.

3. Slight loss in weight and occasional loose or bloody stool was the only subsequent sign of derangement.

4. Animals sacrificed three to seven months later showed various gross and microscopic changes of a permanent nature in the injured bowel.

5. These changes, though not resembling those of human regional enteritis, exhibited some features compatible with a chronic inflammation.

GENERALIZED CAPILLARY AND ARTERIOLAR PLATELET THROMBOSIS*

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DESPITE voluminous literature on the general subject of thrombosis, relatively few cases are recorded of a widespread thrombotic process limited exclusively to capillaries and arterioles. Such an unusual distribution of thrombi has been reported in only 10 cases^{1,2,3,5,6,7,9} over a period of approximately 20 years. Clinically and pathologically these cases have been strikingly similar. In fact, the symptomatology has been so distinctive that the diagnosis may be made ante-mortem in the future. A rapidly progressing hemolytic type of anemia, a rather marked thrombopenia and bizarre non-localizing cerebral manifestations have constituted the salient clinical features. The course has been febrile, terminating in death in from 1 to 3 weeks. Widespread capillary and arteriolar thromboses have been the outstanding autopsy finding. Although Moscheowitz⁷ regarded the thrombi as of the hyalin type, more recent writers^{1,2,3,9} have considered them to be of platelet origin. Petechial hemorrhages have been repeatedly observed but the extent of these hemorrhages has varied considerably from one case to another.

Except for 1 previous case⁹ and the one to be presented here, all of the patients have been females ranging in age from 9 to 66 years. The present case is reported in order to reemphasize the rather uniform clinical pattern of this syndrome and the sequence of events incident to the underlying pathologic process.

Case Report. History. A 66 year old colored man was admitted to the U. S. Naval Hospital in a conscious but aphasic state. The history, as obtained from the patient's

sister, revealed that he had been in good health until 2 days before admission at which time it was noted that his speech was inarticulate. On the day before admission, the patient could not be understood and could only mumble with considerable difficulty. He was unable to write with his right hand although he appeared to have full control of the arm. Drinking liquids became difficult and swallowing solid foods was impossible. The symptoms became progressively worse but from the onset the speech defect was of an intermittent character; on several occasions, a few clear words were spoken only to be followed suddenly by a series of inarticulate grunts.

The past history was essentially non-contributory as far as could be determined. He had suffered partial deafness for 20 years but had had no previous episodes of aphasia or dysphasia. A history of venereal disease could not be elicited and a detailed family history revealed no evidence of familial blood dyscrasias. There had been no exposure to or ingestion of drugs or poisons of any kind.

Physical Examination. The patient was a well-developed, well-nourished, colored male who was conscious, well oriented and cooperative but aphasic. The temperature, pulse and respirations were normal. The systolic blood pressure was 120 mm. of mercury and the diastolic 80 mm. The pulse rate was 84 per minute. Throughout his entire illness, the skin, sclerae, conjunctivae and fundi revealed no evidence of petechial hemorrhages. The heart was not enlarged and there were no murmurs. The lungs were clear to percussion and auscultation. The abdomen was ovoid, non-tender and no masses were palpated.

Bizarre and fleeting neurologic manifestations were of considerable clinical interest and importance. On admission, the only significant finding, aside from the aphasia

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and dysphasia, was diminished but equal strength of arms and legs. Four days later, however, the aphasia had cleared. Abdominal and cremasteric reflexes were absent bilaterally. The Achilles reflex was hypoaactive on the right and absent on the left. Response to pain and touch was entirely absent in the lower extremities. Response to temperature changes in both upper and lower extremities was diminished. There was no muscular weakness. The following day, neurologic examination revealed agrammatism, acoustic and verbal agnosia, ideokinetic apraxia, increased spasticity and reflexes of the right arm with a positive Hoffman sign on the right. The patient was again sensitive to pain, touch and temperature in upper and lower extremities. Throughout the course of illness, these neurologic manifestations occurred in irregular cycles and appeared to wax and wane in intensity.

Laboratory Findings. The red cell count on admission was 1,800,000; hemoglobin, 38%; white cells, 7850 (70% polymorphonuclears, 20% lymphocytes and 3% monocytes). The red cells on direct smear showed marked hypochromia, anisocytosis, poikilocytosis and polychromia. There was 1 normoblast per 100 white blood cells. Other data: volume of packed cells, 20 per 100 cc.; mean corpuscular volume, 111.1 μ m; mean corpuscular hemoglobin, 30.6 μ g. and mean corpuscular hemoglobin concentration, 27.5%; volume index, 1.18; color index, 1.05; saturation index, 0.89. The reticulocyte count was 8.5%. A platelet count was not done but examination of the blood smear revealed a marked decrease of platelets. Following 2 whole blood transfusions, the red cell count rose to 2,300,000, with hemoglobin of 46%. The volume of packed red cells was 20%, with a mean corpuscular volume of 87 μ m. The mean corpuscular hemoglobin was 29 μ g. and the mean corpuscular hemoglobin concentration was 33%. The volume, color and saturation indices were, as before, within normal limits. The urine contained 3 to 5 red and white blood cells per H.P.F. and a trace of albumin was observed. A stool examination revealed no significant findings. A lumbar puncture revealed normal dynamics with no evidence of block on jugular compression. The white cell count was within normal limits and no red cells or xanthochromic fluid were observed. Spinal fluid glucose was 75 mg. %;

chlorides, 766 mg. %; proteins, 35 mg.%. Serologic studies of blood and spinal fluid showed no evidence of syphilis. The icteric index was 13. A cephalin flocculation test was negative after 24 hours but showed 1+ after 48 hours.

Course. The patient was put on a high caloric diet and was given whole blood transfusions of 500 cc. each on 2 successive days. He appeared to improve physically but the mental status remained essentially unchanged. An intermittent fever ranging from 100° to 102° F. developed 3 days after admission and persisted throughout the remainder of his hospital stay. Five days after admission the patient developed urinary retention. Rectal examination failed to reveal an enlarged prostate gland or any rectal mass. The urea nitrogen was 42.8 mg. per 100 cc. with a CO₂ combining power of 38 vol. %. He became incontinent of urine and refused to eat. Coma developed rapidly and the patient expired 10 days after admission to the hospital.

Autopsy (12 hours after death). The body was that of a well-developed, well-nourished 66 year old Negro male, weighing 150 pounds and measuring 5 feet 7 inches in length. No marks, scars, rashes or hemorrhages were observed. The sclerae and mucous membranes were markedly icteric. There was no evidence of edema, engorged vessels or generalized lymphadenopathy. The pleural cavities were free of fluid but a few delicate adhesions were present in the left apex. The pericardial sac contained approximately 100 cc. of clear, straw-colored fluid. The organ relationships in the abdominal cavity were within normal limits.

The heart (335 gm.) showed many small epicardial and endocardial hemorrhages. The chambers were of normal size and they contained both fluid and clotted blood. The valve measurements were within normal limits and all valves appeared essentially normal. The cardiac musculature was muddy brown and flabby. On section, several small areas of hemorrhage, fibrosis and necrosis were present. The right and left ventricular walls were of normal thickness. The coronary arterial system showed moderate atherosclerosis but no thrombi were observed. The great vessels, except for moderate atherosclerosis, were not remarkable.

The combined weight of both lungs was

1050 gm. The external appearance revealed a smooth, mottled grayish red wet surface and crepitus was readily elicited. On section, a few small areas of grayish yel-

low consolidation were present in the left lower lobe. There was moderate congestion of the parenchyma throughout. The pulmonary vessels, bronchi and lymph nodes

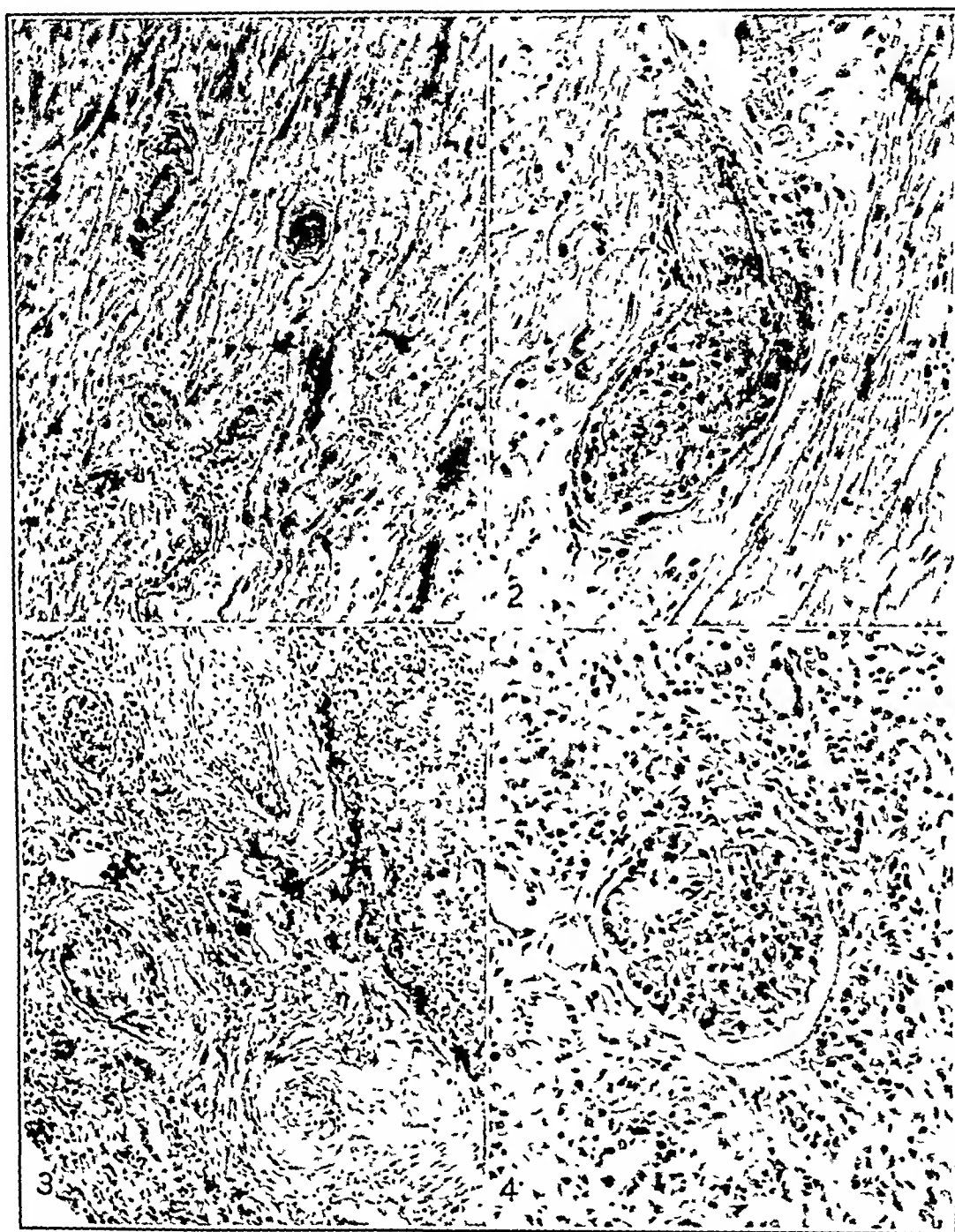


FIG. 1.—Section of myocardium showing thrombosis of capillaries with perivascular fibrosis, cellular infiltration and degeneration of adjacent muscle bundles. Hematoxylin and eosin; $\times 100$.

FIG. 2.—A vessel in the myocardium showing invasion of a platelet thrombus by swollen endothelial cells. Hematoxylin and eosin; $\times 200$.

FIG. 3.—Three vessels in the cortex of the kidney illustrating old dense endothelialized thrombi. Note the endothelial lined spaces bounded by the thrombi and the arteriolar walls. Hematoxylin and eosin; $\times 100$.

FIG. 4.—Kidney showing platelet aggregates in glomerular tuft. Hematoxylin and eosin; $\times 200$.

were not remarkable. The spleen (180 gm.) appeared essentially normal in size, shape and consistency. The pancreas, likewise, showed no significant abnormalities. The liver (1700 gm.) showed a surface everywhere smooth and intact, with the characteristic reddish brown color. On section, the architecture was well preserved but scattered throughout were numerous small petechial hemorrhages. The gall bladder and biliary tract were essentially normal. Multiple submucosal hemorrhages were observed in the stomach but the remainder of the gastro-intestinal tract was not remarkable. The adrenal glands were of normal size and although somewhat congested, showed no definite areas of hemorrhage.

The left kidney (160 gm.) and the right (170 gm.) were similar. The capsule stripped with ease revealing a smooth, reddish brown surface over which numerous small punctate hemorrhages were noted. On section, the cortex was of normal thickness but numerous hemorrhages and small areas of necrosis were observed. The pyramids were well developed and showed no significant abnormalities. The mucosa of the pelvis and calyces was markedly hemorrhagic but there was no evidence of erosion. In the lower pole of the left kidney was a well-circumscribed, firm, gray mass, 4 mm. in diameter. The ureters were slightly dilated and occasional small petechial hemorrhages were observed on the mucosal surfaces. The bladder was moderately dilated and the mucosal surface was markedly hemorrhagic. Multiple small abscesses were observed throughout the prostate and a small pocket of pus, approximately 1 cm. in diameter was present adjacent to the right seminal vesicle. The seminal vesicles, testicles and urethra appeared essentially normal. The skeletal system showed no significant abnormalities and multiple sections through the ribs and vertebra showed red, cellular marrow.

The neck organs were in no way remarkable. The brain weighed 1220 gm. The dura and leptomeninges were everywhere smooth and intact and there was no evidence of hemorrhage. The cerebral and cerebellar hemispheres exhibited the normal contours and the ventricular system was not dilated. There was no evidence of hemorrhage but occasional minute areas of softening were noted throughout the parenchyma. The basilar artery showed rather extensive thick-

ening, tortuosity and atherosclerotic changes.

Postmortem Bacteriology and Blood Chemistry. Blood culture showed no growth; blood non-protein nitrogen, 205 mg. %; urea nitrogen, 103.8 mg. %; creatine, 4.6 mg. %.

Toxicologic Examination. Spectrographic analysis of liver and kidney tissue revealed no abnormally large quantities of any of the poisonous metals.

Microscopic Examination. Heart: The great majority of capillaries and arterioles were occluded with finely granular homogeneous material which had the appearance of conglomerated platelets. No red or white blood cells were noted nor was there any evidence of a lamellated pattern. The endothelial cells lining the occluded vessels were swollen and moderately pleomorphic. Proliferation of these cells was marked but only occasional mitotic figures were observed. In other areas, karyorrhexis and pyknosis of the endothelial cells were conspicuous. Many of these cells could be seen invading and encompassing the platelet thrombi. Many of the vessels were not completely occluded but showed small endothelial lined, crescent shaped spaces usually adjacent to the vessel wall. These spaces did not suggest recanalization but rather incomplete occlusion. Occasional vessels with no thrombi showed moderate swelling of the endothelial cells. In a few areas the vessel walls were ruptured allowing the thrombus material to exude into adjacent connective tissue and cardiac muscle. In some regions, the vessel walls had fused with the thrombotic material causing complete disintegration of the normal vascular architecture. Fibrinoid degeneration of the arteriolar walls was occasionally observed. Many of the thrombosed vessels were surrounded by cuffs of edematous fibrous tissue which contained numerous lymphocytes, plasma cells, histiocytes and occasional polymorphonuclears. No giant cells were present and the lesions bore no resemblance to Aschoff bodies. Many of the muscle cells adjacent to the thrombosed vessels showed degeneration and necrosis. Scattered diffusely throughout the interstitial tissue were small focal clusters of acute and chronic inflammatory cells. In such areas, the tissue was edematous and occasional small masses of fibrin were readily observed. Numerous small areas of infarction were present. Many of the infarcts were recent, while others showed

evidence of healing and fibrosis. The majority, however, were of the low-grade ischemic type. Moderate atheromatous changes were present in the coronary arteries, but no significant abnormalities of the endothelial lining were noted.

Lungs: Many of the alveoli were filled with acute inflammatory exudate. Congestion and edema were noted throughout. The bronchioles were choked with polymorphonuclears and fibrin. Several of the capillaries and arterioles were filled with platelet thrombi but the endothelial changes were not so striking as in the heart. Only an occasional megakaryocyte was seen.

Spleen: The pulp was congested and there was minimal hyperplasia of the Malpighian bodies. Many of the central arterioles and several of the smaller vessels in the trabeculae contained platelet thrombi. A few megakaryocytes were seen but there was no increase of myeloid or erythroid elements.

Genito-urinary tract: Extensive vascular changes were observed. A few of the glomeruli were enlarged and showed increased cellularity. These hyperplastic changes were not striking and no fusion or crescent formation was observed. Many of the capillary tufts and the afferent and efferent arterioles were partially occluded by small granular platelet thrombi. The tubular epithelium in several areas revealed rather extensive degeneration and necrosis. Many of the tubules contained cellular debris and precipitated protein material. Hemosiderin pigment was present in rather large amounts in the epithelium of the collecting tubules. In areas, there was considerable interstitial fibrosis and scarring with distortion of the architecture. Several small wedge shaped hemorrhagic infarcts were observed in the cortex. The majority of the arterioles and capillaries were occluded with platelet thrombi. Fibrinoid degeneration of the arteriolar walls was conspicuous but there was no evidence of inflammation. The endothelial changes were quite similar to those observed in other organs. In addition, the arcuate and interarcuate arteries showed moderate intimal thickening and hyalinization. Large areas of hemorrhage were present in the pelvic mucosa and in the mucosa and submucosa of the ureters and bladder. Examination of the prostate gland revealed numerous confluent abscesses and a moder-

ate degree of hyperplasia. Many platelet thrombi were scattered throughout.

Vertebral marrow: Sections showed numerous islands of erythropoietic tissue consisting largely of pronormoblasts and normoblasts. Cells of the myeloid series were represented in normal proportion. Megakaryocytes were abundant and in many areas there was a slight but definite increase of these cells. The character of the cytoplasm of the megakaryocytes was not distinct, even with Giemsa's stain, because of autolytic changes. Many of the capillaries contained platelet thrombi.

Brain: Scattered diffusely throughout were numerous intracapillary platelet thrombi. Occasional minute areas of encephalomalacia were encountered. No hemorrhage was observed but minimal neuronophagia was noted in some areas. Many of the non-occluded vessels showed abnormal fibrin threads. These threads were greatly thickened and some appeared to be hollow. These abnormal forms appeared to fuse, however, with the normal fibrin threads. Scattered throughout and adhering to the fibrin were small granular masses of platelets. In several of the partially occluded vessels, the thick fibrin threads had fused with platelets to form a homogeneous mass in which the fibrin structure barely could be discerned.

Other organs: Platelet thrombi and occasional areas of hemorrhage were observed in the pancreas, liver, adrenals, gastro-intestinal tract, lymph nodes, thyroid and pituitary glands.

The Thrombotic Lesion. All of the tissues examined revealed large numbers of thrombotic and endothelial lesions in the capillaries and arterioles. These vascular lesions were most marked in the myocardium, kidney cortex, adrenal glands, spleen and brain.

With the routine formalin-fixed hematoxylin and eosin sections, the thrombotic material appeared as a finely granular purplish pink substance that morphologically, at least, suggested platelet origin. In an attempt to determine the precise nature of the thrombotic material, Giemsa, Shorr, Gram-Weigert, iron hematoxylin and iron stains were carried out on formalin and Zenker fixed tissue. These additional staining procedures tentatively substantiated our original interpretation and those of others, that the capillary occlusions were probably

of platelet origin. Neither red cells, disintegration products of red cells, leukocytes or bacteria could be demonstrated in the capillary and arteriolar occlusions. The proliferation and swelling of the endothelial cells and the permeation of the thrombi by these cells was a most remarkable phenomenon. Although occasional non-thrombosed vessels showed minimal endothelial swelling and proliferation, the process was not diffuse; the overwhelming majority of the non-occluded vessels appeared essentially normal. Many of the non-thrombosed vessels contained serum and normal sized delicate threads of precipitated fibrin, but occasional masses of distinctly abnormal fibrin threads were also observed. These threads were 3 to 5 times the thickness of normal fibrin and had the appearance of hollow, non-segmented mycelia. That these bizarre shaped masses were not mycelia was ruled out on morphologic and cultural grounds. Except for the size, the morphologic characteristics and the staining reaction were those of normal fibrin. They were occasionally observed in the newly formed thrombi where platelet aggregates could be seen adhering to them.

Discussion. The genesis of the platelet thrombosis is not known. There is considerable divergence of opinion regarding the fundamental vascular lesion. Altshule¹ speculated that the platelet thrombi were secondary to damaged vascular endothelium. Baehr, Klemperer and Schiffrin² and more recently Bernheim³ felt that there was no definite evidence for primary endothelial damage and that the endothelial changes were secondary to the presence of platelet thrombi. Nothing is to be gained by further speculation over this somewhat controversial point on the basis of morphology alone. There are, however, in this present case 1 or 2 observations that are worthy of consideration. In several of the vascular lesions, particularly in the myocardium, the capillary and arteriolar walls revealed rather marked fibrinoid degeneration and actual necrosis with extrusion of the thrombotic material into the adjacent tissue. Whatever the nature of the toxic agent, if there is such, vascular damage was marked. Such changes occurred only in

vessels which contained platelet thrombi. It is possible that the toxic agent could have been absorbed on the platelet aggregates and that the concentration of the "toxin" was, therefore, greater and more lasting.

Abnormal clotting of the blood is a further possibility which deserves serious consideration from the standpoint of etiology. Although there is no basis for assuming that a defect in the blood clotting mechanism may produce morphologic changes, the abnormal physical nature of some threads of fibrin is perhaps suggestive of such a defect. Regardless of this questionable evidence, there are a number of points in both the stoichiometric and enzymatic phases of the clotting mechanism at which a disturbance of one or more of the components might occur. Excessive clotting as well as acceleration of coagulation is favored by factors which tend to increase the formation of fibrinogen, prothrombin or platelet factor. The stimulation of bone marrow activity with increased production of blood platelets is one such factor, although after a minimal number of platelets is available, this is a rather minor one. Excessive agglutination and disintegration of platelets might be attributed to excessive amounts of the factor deficient in hemophilia. On the other hand, a defect in the platelets may be a qualitative one, that is, a too ready release of thromboplastin from abnormal platelets showered into the blood stream from the bone marrow. Again the abnormal clotting may be due to an inadequacy of the normal antithrombin of the blood thus permitting traces of active thrombin to remain active. The thrombin itself may be abnormal in this regard. In some recent, but as yet unpublished work,⁴ it was discovered that if thrombin be subjected to rather mild denaturation procedures, it becomes refractory to antithrombin activity and yet retains the ability to convert fibrinogen into fibrin. It is conceivable, therefore, that traces of thrombin formed in the blood stream from the conversion of prothrombin might be

altered in such a way that the thrombin no longer would be inactivated by anti-thrombin. Whether or not the vascular lesions are the result of endothelial damage or of some defect in the clotting mechanism, or both, it is undoubtedly true that other well-known mechanical factors play a rôle in the ultimate formation of the thrombi. Otherwise it would be difficult to explain the distribution of the vascular occlusions. The various possibilities suggested are, of course, purely speculative but it is strongly urged that the clotting mechanism be studied carefully when the opportunity presents itself in the form of another case.

As Baehr *et al.*² first suggested, the enormous numbers of platelets enmeshed in the thrombosed vessels throughout the viscera were indeed sufficient to have exhausted the available supply and to have resulted in the thrombocytopenia of the peripheral blood. In the case presented, there was not an excess of megakaryocytes in the lungs or spleen. The bone marrow, on the other hand, did show a slight but definite increase of megakaryocytes. In the majority of cases reported, the numbers of megakaryocytes in the marrow have been within essentially normal limits—as they are in most cases of idiopathic thrombopenic purpura.¹⁰ The marrow responds to the peripheral thrombopenia by increased platelet production from preëxisting megakaryocytes and not necessarily from hyperplasia of megakaryocytes. There is no good evidence to indicate that increased platelet production did not occur in these cases. In fact, it probably did, but the increased production might well fall far below the number used up in the formation of the thrombi. This is certainly reasonable in view of the enormous extent of the capillary and arteriolar bed and the widespread distribution of the lesions. Therefore, there is no reason to assume a depression of platelet production or splenic destruction to account for the thrombopenia.⁶

It has been repeatedly observed, especially by Baehr *et al.*, and Altschule, that

despite the extent of the thromboses, there was little evidence of parenchymal necrosis. In this case, although small areas of infarction were present in the heart and kidneys, the degree and extent of the necrosis were minimal when compared to the myriads of thrombosed vessels. We agree with Bernheim that the lack of significant necrosis may be attributed to incomplete occlusion of the involved vessels and to the lack of involvement of the total capillary bed in a given area. It was mentioned previously that small but definite endothelial lined spaces were present at the periphery of many of the thrombi. Such lesions did not have the appearance of recanalized vessels but suggested incomplete occlusion initially. Indeed, the histologic appearance of a large number of infarcts suggested a prolonged ischemic process indicative of slow or incomplete occlusion.

From a thorough study of the clinical and pathologic material in this case, it is felt that the syndrome is not related to lupus erythematosus disseminata, polyarteritis nodosa, or any of the other diseases of the erythema group. The patient in the case reported above showed no evidence of pericardial and pleural involvement, edema, lymphadenopathy, skin lesions, leukopenia and endocarditis commonly encountered in disseminated lupus. The purpura and the vascular lesions are insufficient criteria which do not justify the attempt to relate this syndrome to disseminated lupus.⁶ Furthermore, the vascular lesions in both disseminated lupus and polyarteritis are considerably different from those observed in this case. Whereas the significant changes in lupus and polyarteritis are to be found in the walls of the blood-vessels, in the syndrome under discussion, platelet thrombosis is the most noteworthy observation. The perivascular inflammatory reaction is not generalized, and where present, it is essentially chronic. In their work on the response of tissues to bacterial filtrates, Shwartzman, Klemperer and Gerber⁸ pointed out the similarity of the vascular lesions in

this syndrome to the alterations observed in the blood-vessels of animals in which the Shwartzman phenomenon had been induced.

Because of the widespread capillary and arteriolar thromboses, biopsy should be a useful adjunct in establishing the diagnosis during life.

Summary. A case of a 66 year old Negro male with marked anemia, thrombopenia and bizarre neurologic manifestations is described.

Generalized capillary and arteriolar platelet thrombosis was the outstanding postmortem finding.

The type and distribution of the vascular lesions are pathognomonic of the disease process and the clinical and pathologic features in the cases reported are strikingly similar.

The cause of the thrombosis is unknown.

Brief discussions of the possible etiologic factors and the differentiation from certain diseases of the erythema group are given.

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HYPOPROTHROMBINEMIC ACTION OF QUININE SULFATE

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THE observation was reported by us⁴ some time ago that quinine sulfate in single daily oral doses of 0.33 gm. induces hypoprothrombinemia which can be prevented by concurrent administration of vitamin K. However, Quick⁶ found that this antimalarial caused no decrease in the prothrombin of the blood. Clark and Spitalny,¹ on the other hand, have recently presented their findings that quinine exhibits prothrombinopenic action. This discrepancy of results prompted us to investigate further the action of quinine on prothrombin activity.

EXPERIMENTAL. *Repetition of Previous Experiments.* Two more subjects were studied following the procedure outlined previously.⁴ Again Russell viper venom "Stypven" was employed as the thromboplastic agent in performing prothrombin time estimations. Both persons responded to a daily dose of 0.33 gm. of quinine sulfate with a distinct prolongation of their respective premedication prothrombin times. Upon discontinuing quinine sulfate the findings approximated the original values promptly. Combined administration of a vitamin K compound (10 mg.)* with quinine sulfate (0.33 gm.) over the period of time in which the latter alone had produced the rise in prothrombin time, prevented the quinine-induced prothrombinopenia. Withdrawal of the vitamin K compound and continuation of quinine sulfate at the same dosage level again elicited a prolongation of the prothrombin time in both subjects.

Comparative Study With Different Thromboplastic Agents. The difference in Quick's and our procedure was that different thromboplastic agents were used in estimating prothrombin times: He employed a tissue extract from rabbit brain and we utilized viper venom. Hence a comparative study on the blood of the same persons was instituted using as thromboplastic agents, viper venom on the one hand and a tissue extract on the other.† The former was employed in accordance with the technique advocated by Page and his associates³ and first described by Fullerton.² In carrying out the tests with the tissue extract Quick's original method was followed.

Five normal female subjects ranging in age from 23 to 65 were chosen. Their nutritional state was satisfactory and they were advised to maintain a well-balanced diet. For these persons, prothrombin time estimations were performed on 3 days, in each instance utilizing both viper venom and the thromboplastic tissue extract. Every test was carried out twice. Averages of the 6 values thus obtained in each case for either thromboplastic agent were calculated and taken for the premedication prothrombin time with that particular thromboplastic agent.

The duplicate assays done with a given thromboplastic material in the individual cases were in agreement within the limits of experimental error. However, as appears from Table 1, great variations were found in the prothrombin times obtained

* The vitamin K compound used in this entire study was 2-methyl-1,4-naphthohydroquinone-diphosphoric acid ester tetrasodium salt, Synkayvite "Roche."

† For the purpose of this comparison it seemed adequate to utilize one of the commercially available, standardized preparations derived from lung tissue.

for the same subjects by using the 2 different thromboplastic agents.

Each person received quinine sulfate in single daily doses of 0.33 gm. by mouth for periods varying from 4 to 11 days. Prothrombin times were estimated at frequent intervals, utilizing both thromboplastic materials in each instance. With viper venom, quinine-induced hypoprothrombinemia became evident after 4 to 9 days, but the corresponding tests performed with thromboplastic tissue extract did not indicate a change of prothrombin activity. Quinine medication was continued until the total intake amounted to 2.64, 3.63, 3.33, 2.97 and 1.32 gm. respectively. The corresponding prolongations of prothrombin time at the end of these courses are listed in Table 2.

been taken. Prothrombin time estimations carried out at frequent intervals with both thromboplastic agents in general yielded values which for the individual persons ranged at the same levels recorded for them with the respective agent in the premedication control period.

The combined quinine sulfate-vitamin K medication was followed immediately by a third experimental phase in which vitamin K was withdrawn but quinine administration continued. Again all 5 subjects responded with another pronounced elevation of their prothrombin times when viper venom was used for performing the estimations, but they exhibited no change when thromboplastic tissue extract was employed.

The accompanying charts portray the

TABLE 1.—PROTHROMBIN TIME WITH VIPER VENOM AND WITH TISSUE EXTRACT

Case No.	Subject	Prothrombin time using viper venom (sec.)	Prothrombin time using tissue extract (sec.)
1	G. L. G.	22 7	13 3
2	E. F.	21 3	13.0
3	E. N.	26 5	13 9
4	M. P.	24 4	13 7
5	E. L.	25 7	14 8

Means of control prothrombin times obtained in 5 subjects by using viper venom and tissue extract respectively as thromboplastic agents.

TABLE 2.—PROLONGATIONS OF PROTHROMBIN TIMES

Case No.	Total quinine sulfate intake	Prothrombin time prolongations (viper venom) (sec.)	Prothrombin time prolongations (tissue extract) (sec.)
1	2 64	12 3	0 7
2	3.63	9 7	0
3	3.33	6 5	2 1
4	2 97	4 4	1 1
5	1 32	10 6	0 2

Prothrombin time prolongations obtained in 5 subjects at the end of course of quinine sulfate administration, using viper venom and tissue extract respectively as thromboplastic agents.

Upon discontinuing quinine sulfate the raised prothrombin times promptly regressed and approximated the respective control values within a few days. Subsequently, each subject was placed on the combined oral medication of 0.33 gm. quinine sulfate and 5 mg. of a vitamin K compound daily (in Case 2 once 0.66 gm. quinine sulfate and 10 mg. of vitamin K were taken inadvertently). This dosage was continued at least over the period of time in which quinine sulfate alone had

experimental procedure, and the results obtained.

Discussion. The findings presented furnish evidence that a prothrombinopenic action of quinine is demonstrable if viper venom is employed as thromboplastic agent, but that no such effect becomes evident if instead, a fast-acting thromboplastic tissue extract is used. The readings obtained with the latter preparation are of the same order of magnitude as those recorded by Quick.⁶ In the 4 sub-

jects he studied, the premedication prothrombin times varied from 11.5 to 12.5 seconds, and the corresponding findings for the 5 persons presented here ranged from 13 to 14.8 seconds, with readings during quinine medication never exceeding 16 seconds.

emic action of quinine. The protective effect of vitamin K against such quinine-induced prothrombinopenia becomes evident from the present findings and those reported previously.⁴

Quick in a recent paper⁵ states with reference to his method of prothrombin

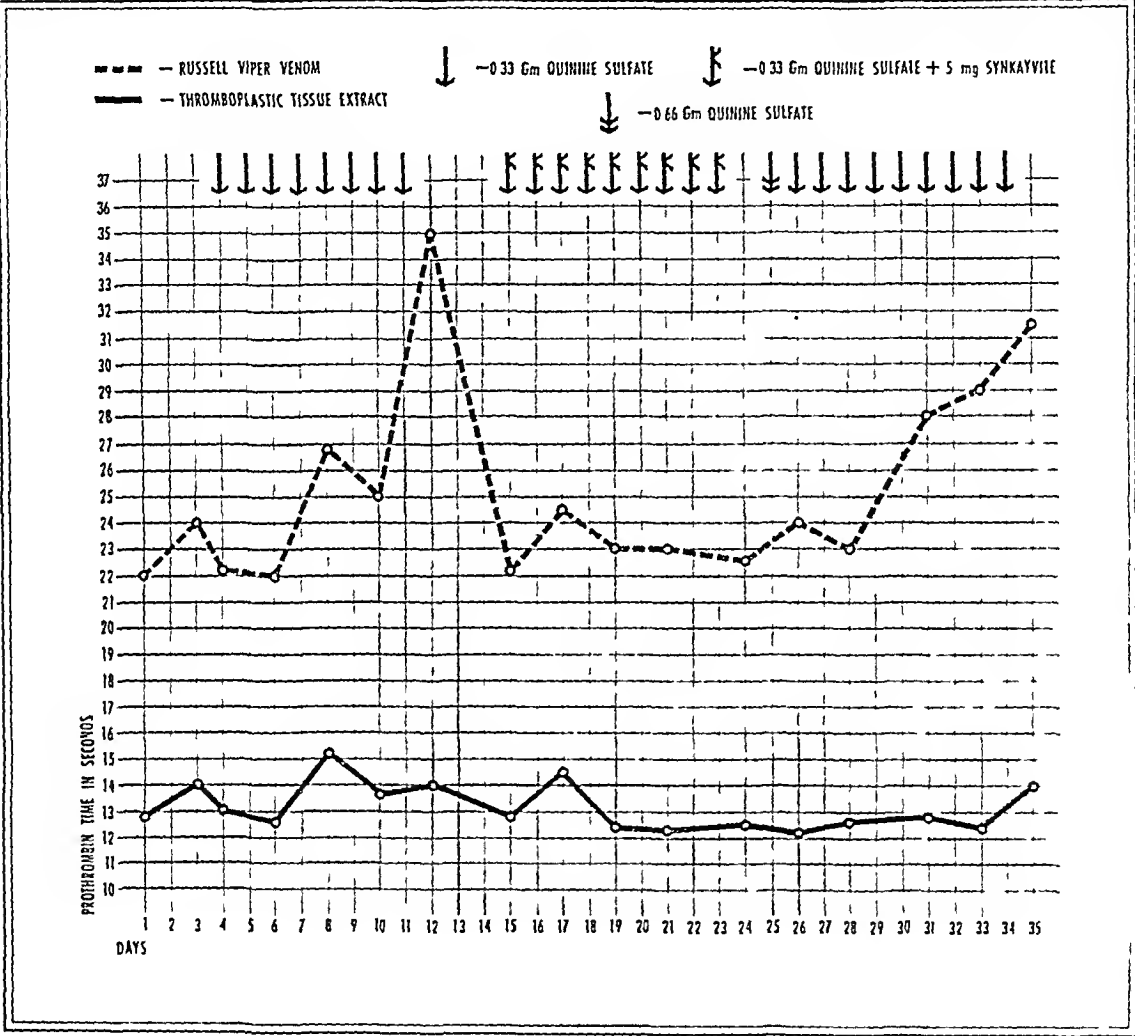


CHART 1.—Effects of quinine sulfate and of quinine sulfate in conjunction with Synkayvite on prothrombin time values obtained with Russell viper venom and a fast-acting thromboplastic tissue extract in G. L. G., a white female, aged 23. In this chart and in Chart 2 it is shown that quinine-induced hypoprothrombinemia is reflected if Russell viper venom is used as the thromboplastin agent, but it is not with a fast-acting thromboplastic tissue extract; concurrent vitamin K administration counteracts quinine-induced prothrombinopenia; continuation of quinine sulfate without vitamin K causes another rise of the prothrombin time if Russell viper venom is employed.

In contrast, premedication values obtained with viper venom in the same individuals varied from 21.3 to 26.5 seconds and showed elevations of as much as 12.3 seconds following the administration of quinine over several days. Such prolongations reflect a hypoprothrombin-

determination that one "cannot detect changes until the prothrombin drops to 50%." This is apparently not so if in place of a fast-acting thromboplastin, an agent of lesser speed, such as viper venom, is used. Then also mild degrees of prothrombin depletion can be demonstrated.

Similarly, in experiments to be reported elsewhere it has been shown that the salicylate-induced hypoprothrombinemia becomes apparent if either viper venom or a slowly acting thromboplastic tissue extract is used but that no prothrombinopenia is demonstrable with a fast-acting thromboplastin. However, as will likewise be reported elsewhere, this fast-act-

observed with viper venom in persons receiving quinine sulfate reflects a prothrombinopenic state, owing to the fact that concurrent vitamin K medication invariably prevents a rise of prothrombin time.

Summary. Additional evidence is presented that quinine sulfate reduces prothrombin activity as gauged by the en-

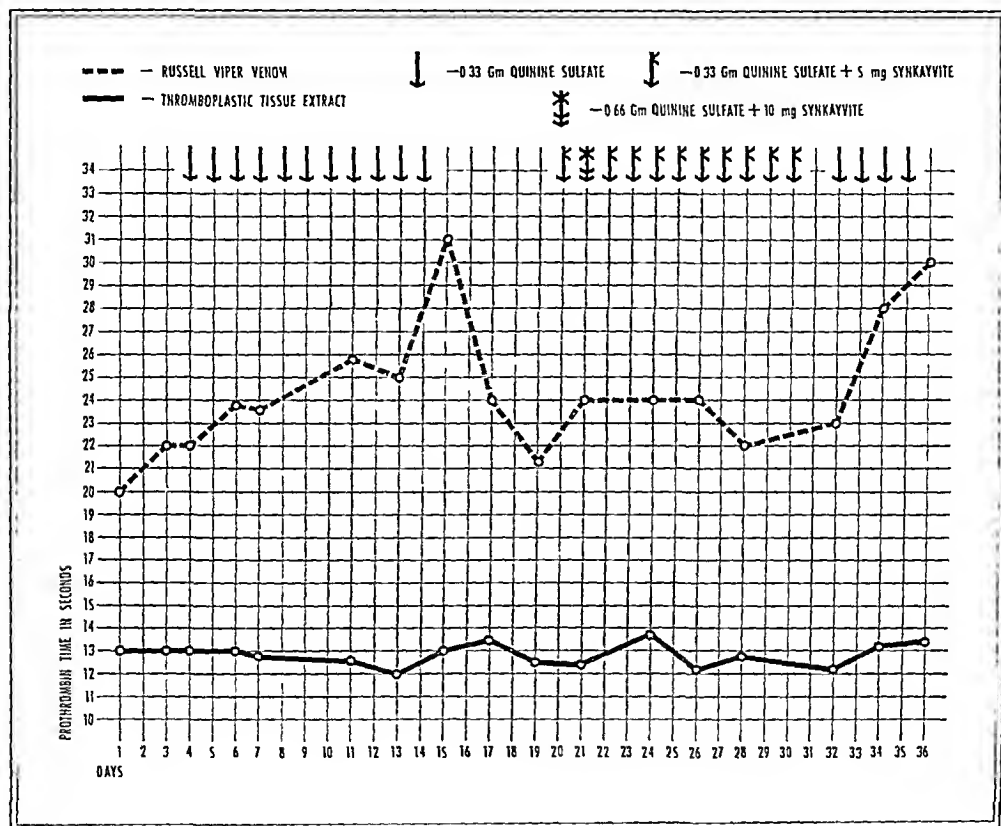


CHART 2.—Effects of quinine sulfate and of quinine sulfate in conjunction with Synkayvite on prothrombin time values obtained with Russell viper venom and a fast-acting thromboplastic tissue extract in E. F., a white female, aged 35.

ing thromboplastic tissue extract reflected a more marked reduction in prothrombin activity in patients receiving dicumarol than did viper venom. Therefore, the possibility must not be overlooked that with different thromboplastic agents, different factors of the complex process of blood coagulation are affected. Notwithstanding, there can be no doubt that an elevation of the prothrombin time as

suining prolongation of prothrombin time if Russell viper venom is used as thromboplastic agent. Quinine-induced hypoprothrombinemia can be prevented by the concurrent administration of vitamin K.

In order to elucidate the discrepancy between these findings and those of Quick, comparative prothrombin time estimations were carried out, employing viper venom on the one hand and a fast-

acting thromboplastic tissue extract on the other. With the former, prothrombinopenia was clearly demonstrable in 5 persons receiving quinine sulfate orally; however, with the latter it was not. The prolongations of the prothrombin time as reflected in the tests with viper venom were counteracted in these subjects if vitamin K was administered with the quinine.

We wish to express our appreciation to Dr. Harry Neivert, who made it possible for us to conduct this work in his laboratory and who exercised supervision over the test subjects. Also we wish to extend our thanks to Dr. Searle of Burroughs-Welch & Co., Inc., New York, who provided the "Stypven" Russell viper venom used for some of the prothrombin estimations.

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ELECTROCARDIOGRAPHIC OBSERVATIONS IN CHRONIC CHOLECYSTITIS BEFORE AND AFTER SURGERY

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It is well established that a relationship exists between gall bladder disease and coronary artery disease. As has been stated by Wolferth,¹⁷ and shown in post-mortem studies by Walsh *et al.*¹⁴ and Breyfogle,⁴ the 2 conditions occur together more often than would be expected from the incidence of each alone. In clinical studies Willius and Fitzpatrick¹⁶ and Schwarz and Herman¹² have noted a similar coincidence of cholecystitis and cardiac affections. The cardiac symptoms of 54% of the patients reported by Willius and Fitzpatrick improved following cholecystectomy. Straus and Hamburger¹³ have described 2 cases with irregular cardiac rhythm that became regular after surgery. Improvement in cardiac symptoms after gall bladder surgery has also been noted by Babcock,¹ Graham and his associates⁷ and Lichty.⁸ Roberts¹¹ reported 5 cases diagnosed as angina pectoris because of typical histories. Subsequently each developed gall bladder colic and underwent cholecystectomy with complete relief of the anginal symptoms as well as the biliary colic. Miller⁹ and Barker and his co-workers² have likewise noted that cardiac symptoms may mimic those of cholecystitis or *vice versa*.

Further indications of the relationship between the 2 conditions are the electrocardiographic abnormalities that not infrequently occur in cholecystitis either with or without cardiac symptoms and the frequency with which they revert toward normal following cholecystectomy, the most common abnormality being depression of the T waves. Fitz-Hugh and Wolferth,⁶ in 1935, reported 6 cases with cardiac symptoms, T wave changes in the

electrocardiogram and cholecystitis, all of which improved following cholecystectomy. Weiss and Hamilton¹⁵ reported 21 patients with cholelithiasis, 4 of whom had abnormal preoperative electrocardiograms. Eight days after cholecystectomy, 3 of the tracings had returned to normal. Inasmuch as 1 of these patients had essential hypertension, the authors concluded that the gall bladder operation had caused improvement in only 2 of the 4 cases, both of those that showed improvement having inverted T waves preoperatively and upright ones 8 days later. Boas and Levy³ and Clarke⁵ each reported a case in which flattened T waves became upright after cholecystectomy. Moschcowitz¹⁰ described a patient whose electrocardiogram showed a prolonged P-R interval preoperatively and a normal one after removal of a diseased gall bladder.

Although these authors have reported electrocardiographic changes, most of the literature has been concerned with clinical changes, and we therefore thought it worthwhile to review the electrocardiograms of the cholecystectomy cases done in this hospital during a 6 year period. The case that prompted us to do this is, I believe, of sufficient interest to warrant reporting it in some detail.

CASE 1. A.M. (No. 1 in Table 1), a 60 year old man, was admitted to the University Hospital in April 1943, because of repeated attacks of severe epigastric pain, associated with abdominal distention and gaseous eructations relieved only by morphine. He also complained of chest pain that developed with exertion or mental perturbation and was relieved by nitroglycerin. Multiple gall stones were seen on radiographic films

TABLE 1.—DATA ON 18 CASES

Case No.	Sex/Age at operation	Preoperative observations			Postoperative observations		
		Cardinal symptoms after oper.	Electrocardiogram	Blood pressure	Operation	Electrocardiogram	Blood pressure
1	M/62	Angina, dyspnea; improved after oper.	3-25-43: diphasic T waves	140/85 (June '44)	Cholecystectomy, 6-1-45 (stones)	6-12-45: sl. flattening of T waves; impr.	150/85 (Jan. '46)
2	F/19	None	4-21-39: low T ₂	164/94 (April '39)	Cholecystectomy, 4-20-39 (stones)	1-12-46: neg.; impr.	152/92 (Jan. '46)
3	F/46	Sl. dyspnea for years; not changed by oper.	3-17-14: low T waves in I, II, CR ₃ and CR ₄	190/120 (Mar. '44)	Cholecystectomy, 3-21-44 (stones)	11-29-45: T waves larger; impr.	182/118 (Nov. '45)
4	F/46	Sl. dyspnea for 2 years; not changed by oper.	12-2-40: T ₃ abnormal	132/88 (Dec. '40)	Cholecystectomy, 12-3-40 (stones)	11-28-45: T waves larger; impr.	142/90 (Nov. '45)
5	F/51	None	8-10-43: small diphasic T waves	122/76 (Aug. '43)	Cholecystectomy, 8-18-43; cholecystectomy, 10-4-43 (stones)	11-29-45: T waves larger, not diphasic; impr.	114/70 (Nov. '45)
6	F/60	None	9-1-43: T waves abnormal	130/88 (Aug. '43)	Cholecystectomy, 9-5-43 (stones)	9-27-45: negative; impr.	114/80 (Sept. '45)
7	F/44	Dysp., dizziness for several years; not changed by oper.	3-21-44: T waves abnormal	190/100 (Dec. '43)	Cholecystectomy, 12-9-43; cholecystectomy, 10-20-44 (stones)	9 20-45: negative; impr.	210/120 (Sept. '45)
8	F/60	Occasional anginal attacks; none since oper.	4-10-45: small and sl. inverted T waves in I and CR ₄ ; flat T waves in II	190/110 (Oct. '44)	Cholecystectomy, 5-4 45 (stones)	8-22-45: sl. but definite impr. in T waves; impr.	160/100 (Aug. '45)
9	F/55	None	3-10-43: T wave changes	155/85 (April '45)	Cholecystectomy, 3 11 43 (stones)	3-43, 8-43, 3-44, 12-44: sl. but definite impr. in T waves; impr.	140/80 (Mar. '44)
10	F/50	Mild dysp., palpitation, and precord. pain; not related to exercise; not changed by oper.	8-27-40: slurred QRS complexes; diphasic T waves; raises question of myocard. infarction	120/85 (Mar. '43)	Cholecystectomy, 5 12 41 (stones)	12-21-43: neg.; impr.; poss. due to healing of an infarct	140/90 (Dec. '43)
11	F/50	Angina, also generalized precord. pain not related to exercise; not changed by oper.	1935 and 1939: poss. old post. infarct; 1940 and 1945: no change	194/98 (Oct. '44)	Cholecystectomy, 5-45 (stones)	12-3-45: no change; unchanged	180/90 (Dec. '45)
12	F/74	Dysp., decompensation; not changed by oper.	3-23-43: auric. fibril., l. bundle branch block, and marked myocard. damage	185/120 (Mar. '43)	Cholecystectomy, 3 20-43 (stones)	7-43, 9-43, 9-44: no change; unchanged	150/70 (Sept. '44)
13	F/53	Weak, palpitation; not changed by oper.	1941, 1942, 1943: r. bundle branch defect	120/90 (1943)	Cholecystectomy, 2-11-44 (stones)	1944, 1945: no change; unchanged	125/85 (1946)
14	F/32	None	2-21-42: diphasic T waves	135/85 (Feb. '42)	Cholecystectomy, 3-3-42 (no stones)	11-10-44: no change; unchanged	152/96 (Nov. '44)
15	M/55	None	4-16-43: slurred QRS complexes; low T waves in I	116/75 (April '43)	Cholecystectomy, 4-21-43 (stones)	11-17-45: further change in T waves; worse	138/72 (Nov. '45)
16	F/17	Dysp., precord. pain; not related to exercise; not changed by oper.	1940, 1943: myocard. abnormality	138/90 (Feb. '43)	Cholecystectomy, 3-1-43 (stones)	9-1-43: further change in T waves; prob. other cardiac damage; worse	150/98 (1944)
17	F/59	Dysp., palpitation; cardiac failure in 1938 and 1939	10-7-38: myocard. damage	222/140 (Oct. '38)	Cholecystectomy, 12-9-38 (stones)	3-2-39: prob. ant. infarct; worse	200/110 (April '39)
18	F/57	Rheum. fever at 6 and 34; 3 anginal attacks per week before oper.; 1 per month after oper.	2-27-45: RST segment and T wave changes; digitalis effects	116/68 (Mar. '45)	Cholecystectomy, 3-28-45 (stones)	11-28-45: digitalis effects mask changes	150/82 (Nov. '45)

and an electrocardiogram showed T wave deformities and extrasystoles. Because of the obvious clinical and roentgenologic evidence of calculous cholecystitis, an operation was recommended. He preferred, however, to try conservative measures and cholecystectomy was not urged.

On a low fat diet he remained relatively free from gall bladder attacks although his angina continued. Late in 1943 he began to lose weight and an electrocardiogram in January 1944 still showed diphasic T waves in Leads I, II and CR₁ with a regular rhythm. With a slight increase in diet the episodes of colic increased in frequency and in April 1945 two attacks occurring within 2 days caused his readmission to the hospital. In view of his continued difficulty, surgery was deemed essential in spite of his cardiac symptoms and a cholecystectomy was done on June 1, 1945. The electrocardiogram taken 6 days prior to operation (Fig. 1A) showed less pronounced changes than any of the previous tracings but it was still definitely abnormal with diphasic T waves. Eleven days postoperatively this had improved so markedly that only slight flattening of the T waves could be seen (Fig. 1B). In the 10 months since June 1945, he has had no attacks of gall bladder colic and only 1 episode of anginal pain, occurring with the excitement of V-J Day. His electrocardiogram, the most recent being April 1946, has remained as it was in the immediate postoperative period; not normal but definitely better than any taken before operation.

In order to determine whether the improvement in this case was unusual, we reviewed the records of 621 unselected gall bladder operations performed in this hospital between September 1938 and December 1944. Only 66 of the patients had had an electrocardiogram within a year prior to operation, and 30 (45%) of these were negative. Of the 36 patients with abnormal electrocardiographic tracings, 17 could be followed. Five of the others had died and 14 could not be traced. The inclusion of the case (A. M.) previously reported in this paper makes a total of 18 patients to be considered. All had pre- and postoperative electrocardiograms and all but 1 had gall stones at operation.

Ten (56%) of that group (Nos. 1 to 10 of Table 1) showed marked improvement in the postoperative electrocardiogram. In No. 10, however, the preoperative abnormality may have been due to a myocardial infarct, the healing of which caused a return of the electrocardiogram to normal. The exclusion of this case, in which the relation to cholecystectomy may have been coincidental, gives 9 cases (50%) that showed electrocardiographic improvement postoperatively because of the surgical procedure. The postoperative tracings of 4 (22%) of the 18 were unchanged, 3 (16%) were worse and 1 (6%) could not be interpreted because of digitalis effects. None of these 10 patients, whose tracings reverted toward normal following surgery, had at any time electrocardiographic evidence of severe myocardial disease although 1 (No. 1) was nearly incapacitated by anginal attacks and another (No. 8) occasionally had such episodes. The first patient has had only 1 anginal attack since cholecystectomy and the other patient has had none.

Six patients (Nos. 11, 12, 13, 16, 17 and 18) had definite cardiac lesions as revealed by their electrocardiograms. After gall bladder operations, electrocardiographic evidence of the cardiac condition progressed in Cases 16 and 17, remained stationary in Cases 11, 12 and 13 and in Case 18 could not be interpreted because of digitalis effects. This latter patient, however, did have less anginal pain after operation.

If a systolic pressure over 170 and/or a diastolic pressure over 100 be regarded as constituting hypertension, then 5 of our patients were hypertensive. The electrocardiogram of 2 of these did not change postoperatively; 2 improved, and 1 became worse. It is possible that the T-wave abnormality noted in these patients was a transient change associated with their elevated blood pressure and that the improvement after surgery was coincidental. Eliminating Case 10 for the reasons already stated, and considering only the remaining 12 patients with nor-

mal blood pressure, 58% (7 cases) showed improvement in the postoperative electrocardiograms, (17%), 2 cases were unchanged, 17% (2 cases) became worse, and 8% (1 case) could not be interpreted because of digitalis effects.

Anginal symptoms were present in only 4 patients (Nos. 1, 8, 11 and 18). Following operation, the first of these improved markedly; 2 others (Nos. 8 and

or suspected cardiac disease. Therefore, the results cannot be strictly applied to all gall bladder cases. However, it is apparent that T wave changes in the electrocardiograms occur not infrequently with cholecystitis, either with or without cardiac symptoms, and, in a number of cases (50% in our series) revert toward normal postoperatively. The cause of the abnormal T waves is not known. At

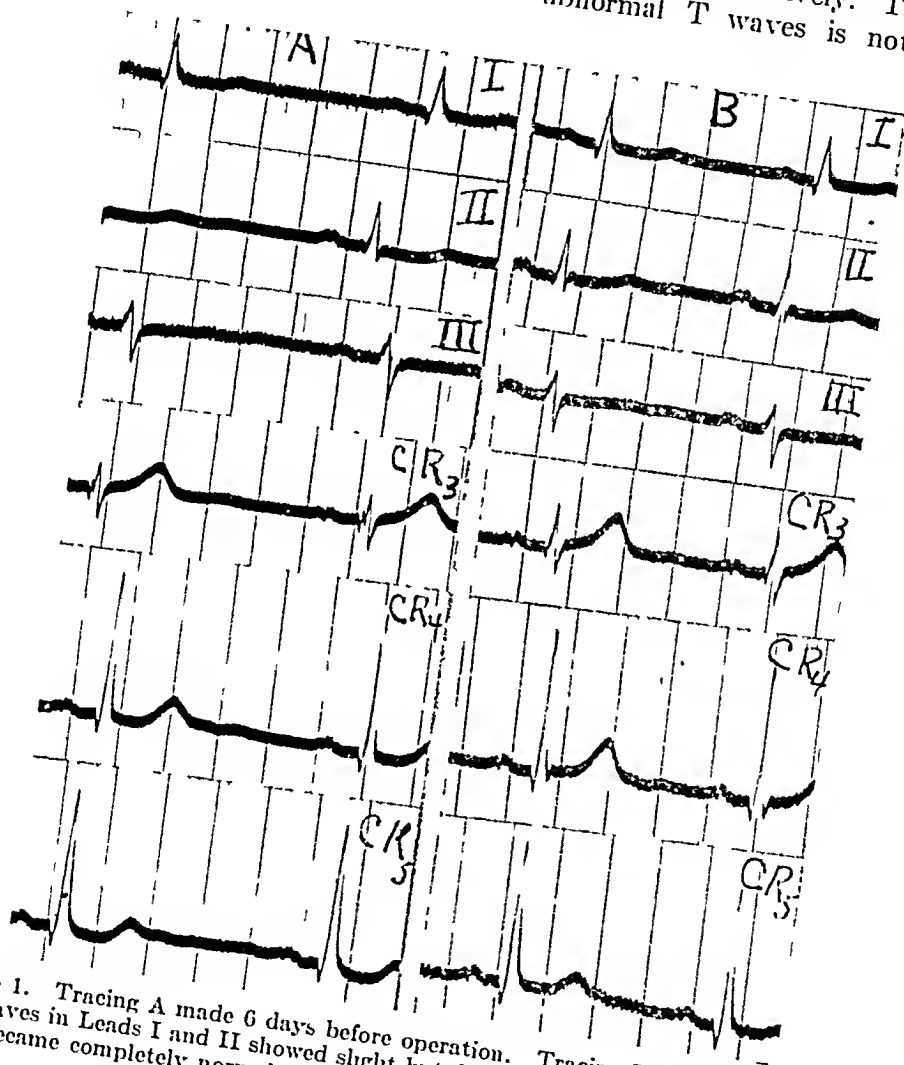


FIG. 1.—Case 1. Tracing A made 6 days before operation. Tracing B made 11 days after operation. The T waves in Leads I and II showed slight but definite changes toward normal and in Leads CR₃ and CR₄ became completely normal.

18) had less frequent episodes; the fourth (No. 11) showed no change in the frequency or severity of her angina, which had always been mild.

To a certain extent the 18 patients reported here are a selected group because electrocardiograms undoubtedly were done only on those surgical patients with known

times they are part of a general picture suggestive of myocardial damage, in which case the need for surgery must be weighed against the cardiac status. However, deformed T waves in cases of cholecystitis do not always reflect heart disease. Possibly they are sometimes due to an abnormal concentration of some substance

arising from perverted biliary tract function. In these cases with no definite cardiac damage, cholecystectomy may well improve the electrocardiogram as well as relieve the gall bladder symptoms and such patients should not be deprived of operation when it is indicated.

Conclusions. We have reported preoperative and postoperative electrocardiographic observations in 17 cases of calculous cholecystitis and in 1 case of non-calculous cholecystitis, all of whom had

abnormal preoperative tracings. Including those with cardiac symptoms as well as those without, 50% showed reversion of the T waves toward normal following gall bladder surgery. Excluding the 5 patients with hypertension did not significantly change this percentage. In view of these results, T wave changes, unless associated with other indications of severe myocardial damage, should not be considered a contraindication to operation in chronic cholecystitis.

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MONOPLÉGIA FOLLOWING CAROTID SINUS PRESSURE IN THE AGED

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SINCE the publication of the classical contributions of Weiss and his co-workers on the clinical significance of hypersensitivity of the carotid sinus, the efforts of other investigators have established the frequency of this condition in older male individuals. Arteriosclerosis, hypertension and congestive heart failure are significant contributing factors, as is also the influence of drugs such as morphine and digitalis. Testing for sensitivity of the carotid sinus has become an important part of the physical examination in any person presenting attacks of syncope or atypical cardiac manifestations. That this procedure may have harmful effects and cause permanent damage has been revealed in several recent publications. To add another example of irreversible cerebral damage following carotid sinus pressure and to discuss the implications of this experience is the purpose of this paper.

Weiss and Baker¹⁷ distinguished 3 forms of reflex response to carotid sinus stimulation: the vagal or cardio-inhibitory, characterized by marked bradycardia, usually with asystole; the depressor, with fall in blood pressure and but slight cardiac slowing; and the cerebral form in which syncopal or convulsive phenomena occur without significant change in heart rate or blood pressure. Mixed forms were recognized and in later papers^{4,18} they were able to separate the cerebral type more completely with the use of atropine to block the vagal response. In these later studies they also demonstrated that simple occlusion of the carotid artery well below the sinus did not elicit the cerebral reactions. They attributed the cerebral response to localized vasoconstriction in reaction to the impulses arising in the carotid sinus. However, they were unable

to find any evidence of diminution of total cerebral blood flow or of cerebral anoxia, such as clearly occurred in the course of the cerebral reactions secondary to the asystolic type. Further evidence against the vasoconstrictor hypothesis was the inability to prevent or modify the cerebral response by the administration of vasodilators, or by inhalation of oxygen. On the other hand, the spinal fluid dynamics observed in the course of the reactions suggested that variations of blood-vessel caliber did occur in the cerebral circulation. Leunox, Gibbs and Gibbs⁸ likewise failed to find any evidence of cerebral anoxia and they attributed the unconsciousness and other direct cerebral phenomena to a purely neural inhibition which they likened to catalepsy and to reflex epilepsy. However, most observers appear to hold to the idea of a local cerebro-vascular response not extensive enough to affect total cerebral blood flow or oxygenation. Numerous electro-encephalographic observations have been made on the cerebral type of carotid sinus reflex and there exists some difference of opinion as to the usual form of brain wave response.^{5,10,14} These studies do not clarify the problem of whether the effect is secondary to circulatory reaction or is primarily neurogenic.

It should be noted that the cerebral phenomena usually observed in the central type of carotid sinus reflex are reversible in character, consisting chiefly of transient unconsciousness or syncope, convulsive movements, or numbness and paresthesias generally referred to the contralateral side of the body. That an irreversible, permanent cerebral effect of carotid sinus stimulation might occur was first suggested by Galdston, Govons, Wor-

tis, Steele and Taylor.⁶ They noted a possible causal relationship between a hyperactive carotid sinus of the vagus type and contralateral complete thrombosis of the common, internal and external carotid arteries with hemiplegia. More direct, and even dramatic, confirmation of this hypothesis was the report of Marmor and Sapirstein¹¹ on the occurrence of a fatally progressive thrombosis of both anterior cerebral arteries following stimulation of the right carotid sinus in a man of 53 years. In this case there was slowing of the pulse without asystole, and clonic twitchings with syncope from which the patient quickly recovered, only to lapse within a few minutes into stupor, with incontinence and a right hemiplegia. Thrombosis of the left anterior cerebral artery was diagnosed. Later the paralysis involved the opposite side as well. At postmortem, recent thrombus formation was found in both anterior cerebral arteries. In this case, too, the thrombotic process in the cerebrum occurred primarily on the side opposite to that of the stimulated sinus and appears to have been induced in the course of the diminished blood flow secondary to the cardio-inhibitory type of carotid sinus reflex. Whether there was an element of the cerebral form of reflex response as well is speculative.

During the 5 year interval since the case report of Marmor and Sapirstein, the sole reference to permanent cerebral effects as a result of carotid sinus pressure is to be found in Levine's textbook, "Clinical Heart Disease."¹² In his discussion of the treatment of paroxysmal auricular tachycardia he notes the occurrence of hemiplegia as a hazard of carotid sinus stimulation in the aged.

The most significant and arresting observations are contained in a recent paper by Askey on hemiplegia following carotid sinus stimulation.¹ As a result of the pooled experience of the California Heart Association, 7 such occurrences are described. This investigator is of the opinion that a direct cerebral reflex occurs with resulting vasoconstriction. In the elderly

and particularly in the presence of cerebral arteriosclerosis this usually reversible phenomenon precipitates a chain of events which leads to occlusion of the vessel by a thrombotic process. In all 7 cases the cerebral hemisphere involved was on the same side as the carotid sinus stimulated. In 2 instances either slight or no cardiac slowing occurred and in these cases at least the hemiplegia could not be explained as due to diminution in total cerebral blood flow secondary to asystole. This point of view is strengthened by the history of recurrent transient hemiplegia in 1 of these patients. This history, together with the evident presence of a hyperactive sinus in all these cases, also argues strongly against the idea that simple carotid artery occlusion was responsible for the cerebro-vascular thrombosis. Hemiplegia occurred on only light massage of the sinus without the possibility of occlusion of the vessel during testing.

These observations indicate that in some of these cases, if not in all, the paralysis represented an irreversible reaction to the cerebral type of carotid sinus hypersensitivity. Askey cites Weiss and his co-workers' earlier observation on the reversible forms in excluding the possibility that simple temporary closure of the carotid might induce the cerebral thrombosis.

However, it must be granted that, although the mechanism most probably depends on the sinus reflex, it may not be so mediated in every instance. Particularly in the aged, obstruction to carotid blood flow may be poorly borne. Ray and Stewart¹³ cite an instance of arteriovenous fistula between the internal carotid artery and the cavernous sinus in a man of 61 years. Pressure on the carotid sinus on the same side induced convulsions and unconsciousness. Procainization of the sinus did not abolish this response, which they then attributed to simple closure of the carotid by pressure. Engel, in discussing the general aspects of syncope, has pointed out that the clinical picture may be modified by preëxistent

structural defects, such as cerebral arteriosclerosis, and that elderly patients may be expected to lose consciousness more quickly and to recover more slowly.²

Previous investigators^{7,16,17} have indicated that hypersensitivity of the carotid sinus mechanism and the clinical syndromes resulting from it occur frequently in old age. A study of the responses to carotid sinus stimulation was undertaken among residents of a home for the aged. One hundred and eighty-eight persons were tested, 106 female and 82 male, with an age range from 62 to 92 years, 22 (12%) showed a response with cardiac asystole. There were 2 instances of the reversible form of cerebral response. In accordance with the warnings of various observers, all patients were tested in the recumbent position. Nonetheless the last subject in the series developed a monoplegia within a few minutes following carotid sinus testing.

Case Report. The patient, a man of 83 years, had suffered from hypertension for many years. The past history was unrelated to the present illness except that he had an old Bell's palsy with residual right facial weakness. The family history was of interest in that the patient's mother had died at 94 years and his father at 79 years of age. At the time of admission to the home, 3 years before the present incident, his blood pressure had been found to be 230/100. Otherwise the physical examination revealed only moderate cardiac enlargement, the chest Roentgen ray showed the heart to be somewhat globular in shape but not definitely enlarged and the aorta elongated. Hemoglobin was 81%; red blood cells, 4,100,000; white blood cells, 5600 (polymorphonuclears, 67%; lymphocytes, 29%; monocytes, 3%; eosinophils, 1%). The blood Wassermann reaction was negative. The urine showed many white blood cells, clumped, and a trace of albumin. Blood glucose was 90 mg. per 100 cc., and the urea nitrogen 13 mg. Subsequent blood pressures ranged from 185/90 to 240/100. On several occasions he had episodes of wheezing dyspnea, usually considered bronchial rather than cardiac in origin. He was placed on digitalis for a short while but was

not taking this, or any other medication, at the time of his carotid sinus test. Electrocardiograms taken over a 3 year period showed chiefly left axis deviation and high voltage of complexes indicative of left ventricular hypertrophy. There was also semi-inversion of T-1 and T-2. The tracings were essentially unchanged over this time.

This individual was included in the group for routine testing of carotid sinus responsiveness. As with the others, he was tested while lying in the supine position on an examining table. Pressure was made first on the right and then on the left carotid sinus area, each side for 15 seconds. There was no response in terms of cardiac slowing or asystole and no noticeable change in heart sounds. No evidence of cerebral response was observed in that there was no syncope, no convulsive phenomena of any kind, no fixation of gaze and no facial pallor as has been so often observed to accompany the cerebral form of response. Almost immediately after this negative test he was allowed to rise from the examining table, and left the room without any assistance. However, within a few minutes our attention was called to him by other residents of the home and he was found nearby, sitting in a chair complaining that his right arm felt heavy. On examination he was unable to raise the right upper extremity, which was in a state of flaccid paralysis. He was placed at bed rest and given vasodilator medication. In the next day or 2 he developed slight drowsiness and dysarthria which rapidly cleared. There was no evidence of involvement of the right lower extremity and no pathologic reflexes were observed. Within several days he was sitting up and not long after he was up and about.

His monoplegia has persisted and he finds it necessary to keep his arm in a sling for comfort. Over a year has passed since the incident, and paresis of the arm still persists. No further cerebral manifestations have been noted.

The experience here recorded, supported as it now is by the observations of others, is evidently not an isolated one. Carotid sinus stimulation can no longer be regarded as an innocuous procedure in the aged or in any patient with evidence of arteriosclerosis or with long-standing hy-

pertension. We are aware that the complications to which we draw attention must be rare. Sigler tested 1886 individuals without any untoward incident.¹⁶ Engel, who has had an extensive experience with carotid sinus stimulation, states: "I am not familiar in my personal experience with any instance of untoward cerebrovascular complication following carotid sinus testing."¹⁷

Despite the rarity of this irreversible reaction, its serious and permanent nature impels us to warn against the casual employment of this test. Others have advised that the test be performed "cautiously" and have recommended that the subject be in the recumbent position. As to the first, it should be pointed out that the reflex mechanism once set in motion cannot be controlled. The sinus is either stimulated or not, but it is impossible to do it cautiously. Our own case demonstrates that the recumbent position will not prevent these unfortunate accidents. This precaution may be helpful in cases of the vagal type by avoidance of syncope and disturbance of cerebral blood flow secondary to asystole but it will not have any effect where the efferent impulse affects the cerebrum or its vessels directly.

Our conclusion must be that the test should be reserved for those cases where it will serve a diagnostic or therapeutic purpose of definite importance. It should not be used as a routine test in patients past 50 years of age. It should not be employed in the elderly to stop attacks of supraventricular tachycardia except in the unusual and obstinate cases where other measures have failed.

An interesting speculation which naturally stems from these observations pertains to the possible rôle of the hypersensitive carotid sinus mechanism in the spontaneous precipitation of cerebral accidents. The cases of Marmor and Sapirstein, and of Askey, and the present instance show that cerebro-vascular thrombosis may occur in response to stimulation of the carotid sinus, whether the hypersensitive mechanism is of the vagal or the cerebral

type. In either case the abnormal arteriosclerotic cerebro-vascular apparatus permits thrombosis when there is a significant disturbance of blood flow, probably together with vasoconstriction.

Recognition of this pathogenetic mechanism as of possible significance in the causation of cerebral accidents suggests the possibility of instituting prophylactic measures in suitable cases. Thus in the elderly, and indeed in all those past 50 years, where hypertension or arteriosclerosis is present, whether cerebral, coronary or peripheral, avoidance of all constriction of the neck should be advised. These patients should be warned against abrupt and violent movements of the neck or head, and against straining at stool or heavy lifting and bending.

Furthermore, consideration should be given to the avoidance of cholinergic drugs such as neostigmin, and particularly morphine and related medications. These agents certainly potentiate the vagal form of the hypersensitive carotid sinus reflex, if not the cerebral. The authors have had an opportunity to observe that carotid sinus pressure often brings a paroxysm of auricular tachycardia to a stop after the administration of morphine, although it was previously ineffective. Digitalis has been found to sensitize the vagal type of reflex^{4,12} and Weiss and co-workers suggest that it may have a similar action in the cerebral form.⁴ We join these authors in warning against unnecessary digitalization as increasing the risk of cerebral complications in the elderly. Weiss and co-workers particularly deplored the routine preoperative use of digitalis in such patients. Rovenstine and Cullen¹⁵ likewise noted the dangers in preoperative use of digitalis or morphine in patients with a hypersensitive carotid sinus, and advised that during the operation, and in the administration of anesthesia, too vigorous manipulation of the head and neck be avoided. In the elderly morphine should be avoided, preoperatively and otherwise, and if used, should always be accompanied by atropine sulfate, $\frac{1}{100}$ gr. It is possible

that atropine should be more widely used in the aged to block the vagal type of hyperactive carotid reflex. It might be included, with benefit, in the commonly used vasodilator combination of theophylline, papaverine and phenobarbital, in the management of patients with arteriosclerosis either with or without hypertension.

Summary. A man, aged 83 years, with long-standing hypertension, developed a permanent right monoplegia within a few minutes after carotid sinus testing. The literature is reviewed with particular

reference to the occurrence of cerebrovascular complications following carotid sinus stimulation. A warning is sounded against the casual employment of carotid sinus pressure either as a diagnostic test or therapeutic measure in aged patients suffering from hypertension and arteriosclerosis. The possible rôle of the hypersensitive carotid sinus reflex in the precipitation of spontaneous cerebral accidents is discussed. On the basis of this hypothesis, suggestions for the prophylaxis of cerebrovascular accidents in the aged are outlined.

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TREATMENT OF CARRIERS OF ENDAMOEBA HISTOLYTICA AND OTHER PROTOZOA WITH CARBARSONE, CHINIOFON AND VIOFORM

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FREQUENCY OF THE CARRIER STATE:
In a previous publication Wenrich, Stabler and Arnett³ found that 4.1% of 1060 students entering a Philadelphia college were symptomless carriers of *E. histolytica*. A later study⁴ revealed an incidence of 11.1% of carriers among 190 food handlers of this institution. A survey of a home for the aged on the outskirts of Philadelphia⁵ revealed an incidence of 11.3% of carriers among 53 inmates and employees. These figures are not to be interpreted as indicating an undue prevalence of *E. histolytica* in the institutions in question or in the city of Philadelphia, but merely as confirming for this locality the opinion of Craig² and others, that 5 to 10% of the population of the United States harbor *E. histolytica* in their intestinal tracts. Other protozoa were, of course, encountered commonly: interest, however, centered around *E. histolytica* because of its potentialities for producing amebic dysentery. It should be emphasized, however, that the work herewith reported applies only to carriers, and not to patients with amebic dysentery. The treatment of the latter disease offers a different, and more difficult problem which will not be dealt with here.

Method and Object of Study. Although we found no evidence that the presence of *E. histolytica* in the stools of our subjects did them any harm, however, it was felt advisable to relieve them of their parasites. To accomplish this, 2 courses of chiniofon or carbarsone were administered to alternate cases during the early part of this study. Later only 1 course was given, and, finally, vioform was given to 12 successive cases. Repeated stool examinations for all protozoa were made before, during and after treatment. Where possible reexaminations were also made at intervals after the treatment had been stopped.

Feces samples, obtained without laxatives, were examined by D. H. Wenrich, Ph.D., and R. M. Stabler, Ph.D., of the Zoölogy Department of the University of Pennsylvania, both as wet preparations and after fixing and staining in the manner referred to in a previous article.¹ The following criteria and terms were adopted: (a) For inclusion in this study, at least 2 positive stools before treatment. (b) For "disappearance," consistently negative stools (at least 2) during treatment or for 1 week thereafter. (c) The term "reappearance" is used to denote the recurrence of 1 or more positive stools after the "disappearance" of the organism has occurred (d). When stool samples were submitted irregularly during the course of treatment, the time of disappearance was assumed to have occurred on the 1st day after the last positive stool.

The dosage of carbarsone was 1 capsule of 0.25 gm. given with breakfast and 1 with supper for 10 days. That of vioform was 1 capsule of 0.25 gm. 3 times daily for 1 week. That of chiniofon was 1 pill of 0.25 gm. 3 times daily after meals on the 1st day, 2 pills after meals on the 2nd day to the 5th, and 3 pills after meals on the 6th and 7th days. When diarrhea or other unpleasant symptoms arose, medication was temporarily discontinued, to be resumed later with the same, or another drug, depending upon circumstances.

RESULTS. *E. Histolytica.* Sixteen *E. histolytica* carriers treated with chiniofon fulfilled the criteria for inclusion in this study. In 4 of these the drug was stopped because of diarrhea. Four other cases complained of lesser degrees of diarrhea not requiring the discontinuance of the drug and the remaining 8 had no symptoms. In 11 of the 12 cases continuing treatment, *E. histolytica* disappeared from the stools in an average of 2.9 days. The 12th case revealed *E. histolytica* 6 days

after the cessation of the first course of treatment, but the organisms disappeared on the 4th day of the second course of chiniofon.

Thirteen persons receiving earbarsone fulfilled the requirements for inclusion. Of these, 1 complained of diarrhea, 1 of diarrhea and dizziness, 1 of constipation and 1 of itching within the rectum. In 1 case the symptoms were sufficiently severe to require temporary discontinuance of the drug. *E. histolytica* disappeared from the stools in 12 cases, the average time required being 1.9 days. In the 13th case *E. histolytica* was found in 3 of 4 specimens submitted before carbarsone was given. Three stools submitted during the first course of earbarsone were negative. After a 10 day rest period during which no stools were submitted, a second course of carbarsone was given and on the 5th day of this course a stool was positive; 42 days later a final sample was submitted which was negative.

Twelve individuals receiving vioform fulfilled the requirements for inclusion. Of these, 1 complained of diarrhea. Here medication would have been changed to another preparation had not the organism disappeared from the stools and no further treatment was deemed necessary. In all cases treatment was successful, the average time required for the disappearance of *E. histolytica* from the stools being 1.7 days.

Other Organisms. Although the presence of protozoa other than *E. histolytica* was not regarded as an indication for treatment, yet while treatment was being administered to the *E. histolytica* carriers, it seemed worth while to record its effects on any other protozoa which happened to be present.

E. coli: Of 4 carriers of *E. coli* the organisms disappeared during chiniofon medication in 3 instances in an average of 3.7 days, but reappeared in 1 of the 3. Of the 6 carriers of *E. coli* receiving carbarsone the organisms disappeared from the stools in all cases in an average of 3.1 days but reappeared in 2 instances.

There were no carriers of *E. coli* in the vioform treated group.

Endolimax nana: This organism was present in 5 individuals in the group treated with chiniofon, but in only 2 of them did the organisms disappear from the stools, the average time being 6 days. In 1 of these endolimax reappeared after treatment was stopped. In the carbarsone treated group 7 revealed endolimax which disappeared from the stools in all cases in an average of 2.9 days, but reappeared in 2 cases. In 5 of the vioform treated group endolimax disappeared from the stools in an average of 1 day, but all reappeared after treatment had been stopped.

Diendamoeba fragilis was present in 2 of the chiniofon treated group, disappeared in an average of 4 days and reappeared in 1 instance. It was present in neither the carbarsone nor vioform treated groups.

Iodameba was present in the carbarsone treated group only, occurred but once, and disappeared in 3 days without reappearing.

Giardia was present in 2 of the chiniofon treated cases, and disappeared 5 days after treatment was begun in 1 of these. The other case did not become negative on 15 tablets (3.7 gm.) of chiniofon; this drug was discontinued because of the appearance of diarrhea. A subsequent course of carbarsone resulted in the disappearance of giardia without recurrence.

Chilomastix: Of 2 instances of chilomastix infestation the organism disappeared on the 2nd day after the administration of vioform was begun in 1 instance, but later reappeared. In the 2nd instance the organism disappeared 3 days after the administration of carbarsone, the data being insufficient to indicate whether or not there was any reappearance.

Summary. 1. Chiniofon, carbarsone and vioform all proved efficient in ridding apparently healthy carriers of *E. histolytica*.

2. These drugs did not prove as efficient in eliminating other protozoa from the stools.

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PROGRESS OF MEDICAL SCIENCE

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THE PRESENT STATUS OF TRYPARSAMIDE IN SYPHILOTHERAPY

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IN evaluating any drug, 2 primary questions arise: (1) the toxicity of the agent; and (2) its therapeutic efficacy. An additional problem in pharmacotherapeutics is the comparison of the drug under consideration with other agents in terms of toxicity and efficacy.

Tryparsamide, a pentavalent arsenical, was synthesized by Jacobs and Heidelberger in 1919.¹² Pearce and Brown²³ observed that it had very little effect on the spirochetes in the lesions of experimental rabbit syphilis. Moore and his associates²⁰ were unable to influence the course of infectious syphilis in patients. There was no regression of the skin manifestations of 6 patients with infectious syphilis, and in 3 the *T. pallidum* was demonstrable on repeated dark-field examinations. Dubois⁶ followed a patient who developed a chancre while receiving weekly injections of tryparsamide for chronic trypanosomiasis. The spirochetes flourished during the arsenotherapy and the drug had no apparent effect on the course of the syphilis. The inability of tryparsamide to influence either the spirochetes or

lesions of infectious syphilis is apparent from these few observations.

Pharmacology. The assumption is well supported that organic arsenicals are therapeutically active by virtue of their ability to inhibit essential metabolic processes of the parasite. Voegtlin, Dyer and Leonard³³ and later Rosenthal²⁶ suggested that trivalent arsenicals unite with the cytoplasmic sulfhydryl (SH) groups of the organism. These workers presented evidence that the activity of the pentavalent group depends on the ability of the tissues to reduce the drugs of higher valency to the trivalent form. Recently Hogan and Eagle¹¹ have suggested that the therapeutic value of an arsenical compound is proportional to the amount clinically bound by the pathogen. It was found that trivalent arsenicals are bound by tissues to a greater degree than are the pentavalent compounds. The amount of arsenical remaining in the tissues after injection of 700 mg. of tryparsamide was of the same order of magnitude as after injection of 0.8 mg. of phenyl arsenoxide (trivalent arsenical). This suggests that

the affinity for animal tissues is 900 times greater for arsenoxide than for tryparsamide.

Lorenz¹⁷ found that between 80 and 90% of tryparsamide is excreted within 1 day following intravenous injection. Young and Muehlberger³⁹ noted that between 88 and 95% of tryparsamide is excreted in the urine within 24 hours and much of the drug is recovered *unchanged*. In contrast, Voegtlin and Thompson³⁴ recorded that arsenoxide is tenaciously retained in the body cell. These observations confirmed the analysis of Young and Hamilton³⁸ who found that much of tryparsamide is excreted in the urine as such within 6 hours of an intravenous injection. *Hogan and Eagle showed that arsenicals* poorly bound by tissues (as tryparsamide) are rapidly excreted, whereas those compounds firmly held in the tissues (as trivalent arsenicals) were excreted at a correspondingly slower rate. In the case of tryparsamide 40% is eliminated from the body within 1 hour. These observations make it apparent that there is little opportunity for the pentavalent arsenicals to be utilized therapeutically.

In spite of the obviously low trepanemicidal effect of tryparsamide, it has been postulated that the drug hastens recovery in neurosyphilis because of a greater penetrability of the central nervous system. This concept is based primarily on the work of Voegtlin, Smith, Dyer and Thompson,³² who injected trypanosomes into the subarachnoid space of rabbits. Subsequently, various arsenicals, including tryparsamide, were administered intravenously, and 24 hours later the subarachnoid fluid was examined for trypanosomes. It was found that tryparsamide had the greatest trypanocidal effect, and sulfarsphenamine was almost as effective. This was interpreted as evidence of greater permeability of the meninges by the pentavalent drug. These experiments of Voegtlin and his associates have been accepted as evidence for the superiority of tryparsamide over the trivalent arsenicals for treatment of

neurosyphilis. The greater vulnerability of the trypanosomes to tryparsamide as a specific agent has not been taken into consideration, nor has any effect been made to differentiate between penetration of the meninges and penetration of the nervous tissue.

Cornwall and his associates³ found that less arsenic may be recovered from the spinal fluid following an injection of tryparsamide than after arsphenamine, neoarsphenamine or silver arsphenamine. In fact, for comparable amounts, 24 times more arsenic was obtained from the spinal fluid after an injection of silver arsphenamine than after tryparsamide. Fordyce and Myers⁹ observed that the brains of mice contained 9 times more arsenic after an injection of silver arsphenamine than after tryparsamide, although the amount of silver arsphenamine, a trivalent arsenical, was only one-fifteenth the amount of the pentavalent material. The workers concluded that "tryparsamide does not possess an unusual power of arsenic penetration into the central nervous system. Therapeutic penetration is hypothetical in that other factors which may enter into this condition are not available either experimentally or clinically." Von Kennell and Kimmig²⁵ were unable to recover any arsenic from the spinal fluid of patients treated with solvarsin, a pentavalent arsenical similar to tryparsamide.

From the experimental data, there is little satisfactory evidence that tryparsamide possesses either greater penetrability or affinity for the central nervous system than the trivalent arsenicals. When the clinical observation, that tryparsamide is unable to influence either the lesions or spirochetes in infectious syphilis, is added to the pharmacologic material cited, one would not anticipate that the drug will be a powerful agent for the treatment of neurosyphilis.

Toxicity. Following the introduction of tryparsamide, relatively few constitutional reactions were reported. Nitritoid crises and gastro-intestinal complaints were virtually unknown. Kopp and Solomon,¹²

in a review of their cases, found a definite increase in reactions from 1923 to 1939. In more recent years, 8.6% of the patients experienced nitritoid crises, whereas from 1923 to 1937 these reactions were less than 3%. Gastro-intestinal symptoms increased from approximately 1 to 7.1%. These workers also noted skin lesions, often of an urticarial nature, chills and fever drowsiness, tremors, emotional upset, dizziness, headaches and, more rarely, transient peripheral nerve damage, visual and auditory hallucinations, convulsions and coma. These complications often did not appear until after extensive treatment. Traenkle and Dulce³⁰ described liver necrosis in 2 patients after tryparsamide therapy. Because nitritoid crises were considered so rare in 1938, case reports were made by Astrachan and Franks,¹ Cormia,² and Levy.¹⁶ Downs and his associates⁶ found that 13.5% of their patients developed nitritoid crises after tryparsamide, and a smaller group developed gastro-intestinal complaints. Moore¹⁹ recorded a definite increase in toxic manifestations and suggested the possibility that impurities in recent manufacture might be responsible.

Optic nerve damage was observed by the first clinicians to use tryparsamide therapeutically. Pearce²² treated 77 patients for trypanosomiasis and found 17 instances of visual complaint. Ten recovered completely, but in 7 permanent nerve destruction occurred. Lorenz and his associates¹⁸ found that 40% of their patients developed evidence of toxic amblyopia as a dosage of 5 gm. of tryparsamide weekly. Woods and Moore³⁷ followed 241 patients treated once weekly with 3 gm. of the drug, and observed that 94% of reactions occurred between the first and tenth intravenous injection. Of the entire group, of patients, 5.5% developed objective evidence of damage to the optic nerve, and an additional 10% complained of visual disturbances. Patients with tabes dorsalis and general paresis were especially prone to develop restricted visual fields. This was observed in 23% of the patients

with these serious manifestations of syphilis, whereas in patients without evidence of neurosyphilis, damage was detected in 6.2%.

Sloan and Woods²⁷ studied this problem and found 5.3% of 2087 patients experienced subjective symptoms after tryparsamide treatment. These complaints were "dazzling, shimmering or a glare as produced by bright light on snow." These symptoms usually began after several injections of the drug, but occasionally began after the first few treatments. The subjective complaints were often transient, lasting from a few hours to a few weeks. Of the group of 2087 patients, 71 (3.4%) subsequently showed objective evidence of permanent optic nerve damage consisting of constriction of the visual fields. Powell and Smith²⁴ studied 16 patients for detailed changes following tryparsamide therapy. Visual fields were done prior to each injection, and it was found that 11 of the 16 patients developed definite constrictions of the peripheral fields between the third and eleventh treatment. None of the patients had any evidence of optic nerve damage prior to the institution of therapy.

Kopp and Solomon¹³ noted that the type of syphilitic lesions may bear some relationship to susceptibility to visual disturbance. In their series, 24% of the parietic group and 43% of the tabetic group developed eye complications, but none of the patients with meningovascular syphilis were handicapped.

Therapeutic Efficacy of Tryparsamide. The first report on the use of tryparsamide was made by Lorenz and his associates¹⁸ in 1923. They found that 7 of 12 cases of early paresis and 21 of 42 cases with advanced paresis improved greatly and were able to return to work. However, some of the cases relapsed, and it was found that recovery was not permanent unless mercury was added as a therapeutic agent. This is both the first and the most enthusiastic report in the literature. The following year, Moore, Robinson and Keidel²⁰ described their results in 27 cases

of paresis, in 6 patients with tabes, and in 8 patients with asymptomatic neurosyphilis. This series differs appreciably in 2 important respects from that reported by Lorenz. Only 2 of the 40 cases, including the paretics, were sufficiently ill to require hospitalization. Also, the authors write that "secondly, 32 of the 40 cases had already been subjected to prolonged and intensive antisyphilitic treatment, sometimes with intraspinal therapy, though symptoms and physical signs had often already disappeared before tryparsamide was begun." However, the authors go on to say, "In spite of these differences in material and procedure, our results are in essential agreement with those of Lorenz and his co-workers." Four patients in the series with negative serologic tests for syphilis developed positive reactions while undergoing tryparsamide therapy.

In 1924, Moore and his associates²¹ again reported favorably on the efficacy of tryparsamide, considering it of particular value in general paresis, meningovascular syphilis and the majority of cases with tabes dorsalis. Solomon and Viets²⁹ reported that tryparsamide was approximately as valuable as trivalent arsenicals in treatment of meningovascular syphilis, of little benefit in tabes dorsalis, and helped a small number of cases with general paresis.

When Lorenz reviewed his earlier work in 1928, he found that the therapeutic results were satisfactory after 5 years in 87% of the cases of neurosyphilis, when mercury had been added to the tryparsamide therapy. No reference is made to symptomatic and asymptomatic cases. Reesc,²⁵ in 1933, reviewed the earlier work done by Lorenz and his associates. He reported that tryparsamide must be used over a period of years to be effective. Reese added, "At the onset we used tryparsamide without any antisyphilitic medication, but the noted beneficial effect on the clinical and serologic picture remained stationary, especially with regard to the clinical improvement. The addition of mercury resulted in more permanent im-

provement of the serologic findings, as well as a more rapid prolonged clinical benefit." The Wisconsin group claimed clinical arrest or remission in 54% of general paresis and 78% of the meningovascular syphilis. Patients with tabes dorsalis with lancinating pains, urinary disturbances and impotency were often relieved. Ebaugh and Dixon⁷ reported that among 52 paretics marked improvement was obtained in 15 cases. Wile and Wieder²⁶ reported on a group of patients treated with tryparsamide. They found improvement in cells and protein of the cerebrospinal fluid, but little change in the colloidal gold or Wassermann reaction. They noted clinical improvement in but 7 of 32 paretics, 2 of 7 tabetics, and 2 of 12 taboparetics. From these data they assumed that tryparsamide could be expected to be of value in one-third of the patients with neurosyphilis.

Solomon and Epstein²⁸ reported on 81 patients with general paresis and found that they could arrest the deterioration in 42%, and that in the remaining 58% the process was uninfluenced. The spinal fluid became normal in 26.7% between 1 and 9 years after tryparsamide therapy was begun. Seventeen patients who failed to respond to tryparsamide obtained striking benefits from malaria. The authors concluded that "the clinical results of treatment with tryparsamide do not differ greatly from those obtained by malarial therapy." Because general paresis is invariably a fatal disease, these reports cannot be discounted.

Hinrichsen¹⁰ reviewed the results of many writers and learned that, although as high as 50% remissions were reported with early paresis, only 22.5% of advanced cases improved. Since the results in the advanced cases varied from zero to 80%, these figures must necessarily be viewed with skepticism.

Lees¹⁵ described excellent results in tabes dorsalis in 200 patients who received 2 years of combined tryparsamide and bismuth therapy. He noted reduction in sensory disturbances in 78%, diminution

of ataxia in 65 %, and alleviation of bladder difficulties and gastric crises in an undisclosed number. Dattner⁴ finds his own experiences at great variance from those of Lees, and believes tryparsamide of little value in eliminating tabetic symptoms. In the review by Hinrichsen, various authors claim improvement in 20 to 75 % of patients with symptoms of *tabes dorsalis*.

Clinical Study. There are registered in the Syphilis Clinic of the New York Hospital 736 patients with asymptomatic neurosyphilis and 355 patients with *tabes dorsalis*. All of these cases have been reviewed in an effort to evaluate the toxicity and therapeutic efficacy of tryparsamide.

Toxicity. Study of the group with asymptomatic neurosyphilis revealed that 206 patients were followed an average period of 6.1 years, and at least 2 specimens of cerebrospinal fluid were obtained 1 or more years apart. Of this group of 206 asymptomatic patients, 139 received tryparsamide at some time during their course of antisyphilitic treatment. Sixty patients (43 %) developed toxic reaction of such a degree that tryparsamide injections had to be discontinued. There were 15 instances of minor reactions, including 11 cases of nitritoid crisis and 4 patients who experienced gastro-intestinal upsets, characterized by nausea and vomiting.

It has been customary in this clinic to obtain an ophthalmologic consultation prior to the initiation of tryparsamide therapy. This examination routinely includes examination of the optic nerve, determination of corrected visual acuity and plotting of peripheral fields. If a patient complained of subjective evidence of toxicity, as photophobia, glaring or "fuzzy" vision, treatment was interrupted until the patient could be reevaluated by the ophthalmologist. Patients who were reported as showing pallor of the disk or decrease in visual fields or optic nerve damage due to any cause as severe glaucoma or retrobulbar neuritis were not permitted to have tryparsamide again. In spite of these detailed precautions,

45 patients of the 139 who received tryparsamide (32 %) developed subjective evidence of optic nerve sensitivity to the pentavalent drug, and subsequent studies showed that in 17 instances there was definite and permanent visual damage. These 17 patients with permanent visual damage represent 12 % of all patients with asymptomatic neurosyphilis who receive one or more injections of tryparsamide.

Of the 355 patients with *tabes dorsalis*, 202 were suitable for study. This group was followed for an average of 5.8 years, and, of these, 126 received tryparsamide at some period during their course of antisyphilitic treatment. There were 22 instances of minor reactions, including 10 examples of nitritoid crises, 5 patients who had gastro-intestinal upsets, and 4 patients with dermatitis, plus 3 who experienced other minor disturbances; 47 % of the tabetic group (59 of 126) who received tryparsamide developed subjective symptoms of injury to the optic nerve. Subsequent evaluation of these 59 patients revealed that 27 progressed to objective evidence of optic atrophy with some pallor of the disks and reduction in the peripheral visual fields; 27 patients recovered entirely, but the fate of 5 cannot be determined because of their failure to return to the clinic. It is apparent, then, that of the 126 tabetics who were exposed to tryparsamide therapy, at least 21 % (27 of 126 patients) developed impaired vision. The toxicity of tryparsamide in patients with asymptomatic neurosyphilis and in *tabes dorsalis* is summarized in Table 1. No effort was made to evaluate the damage done in general paresis, because often these patients, in the presence of the psychosis, are unable to protest minor visual changes before excessive harm has been done.

Inefficacy of Tryparsamide. In the present study, only patients with asymptomatic neurosyphilis and *tabes dorsalis* are considered. Evaluation of patients with meningovascular syphilis is difficult because the group is heterogeneous and

patients often improve spontaneously. Almost every patient with general paresis in the New York Hospital Clinic received either malaria or penicillin therapy, and consequently this group is not studied.

In spite of the frequency of overlapping treatment schedules which include trivalent arsenicals as well as bismuth in the present series of patients reported, it appears that the addition of tryparsamide did not improve the patient's opportunity for a successful outcome. This is demonstrated by the fact that the failure rate is not increased in those patients who did not receive tryparsamide. Furthermore, those patients who received either malaria or penicillin did appreciably better than those who received arsenotherapy.

jections of the drug. There was definite improvement in the cerebrospinal fluid of 62 of these patients, and of these all but 5 patients, or 57, had received in addition 75 injections of trivalent arsenicals and bismuth, and several had a course of malaria therapy. There were 38 patients (38%) who failed to improve.

There were 122 patients who received no tryparsamide but had a minimum of 75 injections of trivalent arsenicals, including old arsphenamine, neoarsphenamine and arsenoxide, plus bismuth; 86 patients (70%) improved. A total of 36 patients (30%) failed to exhibit satisfactory cerebrospinal fluid changes. In essence, these patients received the same trivalent arsenotherapy and bismuth as

TABLE 1.—TOXICITY OF TRYPARSAMIDE

Type of neurosyphilis	Patients treated	Minor reactions*	Visual reactions		Total reactions
			Transient	Permanent	
Asymptomatic . . .	139	15 (11%)	28 (20%)	17 (12%)	60 (43%)
Tabes dorsalis . . .	126	22 (17%)	32 (25%)	27 (21%)	81 (64%)

* Includes nitritoid crises, gastro-intestinal and cutaneous reactions.

ASYMPTOMATIC NEUROSYPHILIS. In the evaluating of any therapeutic agent in the treatment of asymptomatic neurosyphilis, 2 factors must be considered: (1) the ability of the treatment to induce changes of the various cerebrospinal fluid components toward normal; and (2) maintenance of the asymptomatic state, that is, prevention of clinical evidence of symptomatic neurosyphilis.

Laboratory Evaluation. Because of the frequency of overlapping treatment schedules, each chart was evaluated as follows:

(a) Was cerebrospinal fluid improved on 25 or more injections of tryparsamide.

(b) Did cerebrospinal fluid fail to improve on 25 or more injections of tryparsamide.

(c) Of those who improved on the tryparsamide therapy, how many received an additional course of at least 75 injections of trivalent arsenical and bismuth.

Of the 139 patients in the asymptomatic neurosyphilis group who received tryparsamide, 100 patients received at least 25 in-

jections of the drug. There was definite improvement in the cerebrospinal fluid of 62% of those who received tryparsamide, in contrast to the 70% who did not receive it. This indicates that those patients who received the pentavalent drug and risked the toxicity associated with it, did not have any greater chance of successful outcome.

Twenty-six patients with asymptomatic neurosyphilis underwent a course of malaria therapy with subsequent improvement in the cerebrospinal fluid of 21, a failure rate of 19%. In the malaria treated series, evaluation was done prior to the initiation of chemotherapy.

In a recent study undertaken at this hospital,¹⁴ 34 patients with asymptomatic neurosyphilis were treated with sodium penicillin. Most of these patients received 4 million units of the drug during a 2 weeks period. Many had failed to respond to previous antisyphilitic therapy.

It was found that, of the 34 patients, all but 5 had responded satisfactorily; 1 year after instituting penicillin therapy, the cells, protein, and colloidal gold curve were normal, and the titer of the Wassermann reaction had dropped appreciably. The failure rate is 15%. This should be compared to the failure rate of 19% after malaria therapy, of 30% following trivalent arsenobismuth therapy, and of 36% in patients who received tryparsamide in addition to the trivalent arsenotherapy. Although it is impossible to determine the exact worth of tryparsamide from these data, it is readily apparent that the addition of the pentavalent drug did not help the patients who received it.

Clinical Evaluation. Determination of the therapeutic value of any agent used in asymptomatic neurosyphilis is essentially an evaluation of its ability to induce changes in the cerebrospinal fluid, except for subsequent studies to determine how many patients developed symptomatic neurosyphilis. Very few patients of those followed developed clinical evidence of neurosyphilis. One reason for this may be that almost all patients with a strongly positive cerebrospinal fluid (elevation of the cell count, total protein and colloidal gold curve) were given either malaria or penicillin. This vigorous attack on those patients who were the more like candidates for clinical neurosyphilis precludes any analysis of the comparative value of the antisiphilitic agents used. For the most part, patients who received tryparsamide and trivalent arsenicals had relatively inactive cerebrospinal fluids with essentially normal cells, protein and gold curve.

TABES DORSALIS. *Laboratory Evaluation.* Of 81 patients with tabes dorsalis treated with 25 or more injections of tryparsamide, there was no improvement in the cerebrospinal fluids of 34 (42%). There were 109 tabetic patients who received at least 75 injections of trivalent arsenical and bismuth without tryparsamide. Of this group, 42 did not improve (38%). The same statement may be

made about those patients with tabes dorsalis that was made about the group with asymptomatic neurosyphilis; namely, that the group who had tryparsamide received approximately the same amount of trivalent arsenobismuth therapy as the group who did not receive tryparsamide. Again, the number of failures is approximately the same (42% with tryparsamide and 38% without tryparsamide). It may be concluded that tryparsamide had no more influence in the cerebrospinal fluid in patients with tabes dorsalis than it did in patients with asymptomatic neurosyphilis.

A total of 50 patients were given a course of malaria with no subsequent improvement in the cerebrospinal fluid of 14 (28%). In the penicillin treated group of tabetics, there were 22 patients who received 4 million units and were followed at least 12 months. All but 3 cases obtained a satisfactory cerebrospinal fluid response, a failure rate of 14%.

Clinical Evaluation. The ability of tryparsamide and of other antisiphilitic agents to influence the complaints of tabes dorsalis is considered. These symptoms include shooting pains, ataxia, urinary incontinence, diplopia, gastric crises and sexual impotency. Trophic changes, such as Charcot joints and skin ulcers, are not included. Detailed evaluation will appear in a subsequent publication. At present, these symptoms are grouped according to the therapy administered. There were a total of 84 symptoms among the 81 patients who received 25 or more injections of tryparsamide. There was no alleviation of 54 symptoms (64%). When the group of patients who received only 75 injections of combined arsenobismuth therapy and no tryparsamide therapy was investigated, it was found that 67 of 135 symptoms (50%) were undiminished. A smaller group of patients who received malaria complained of 51 symptoms; 18 complaints were unaltered (35%). In the group who received 4 or more million units of penicillin, there were 65 complaints, with no improvement

in 23 (33%). The ability of tryparsamide to relieve symptoms in *tabes dorsalis* is no greater and probably is less than that of other forms of antisyphilitic therapy. Many patients who were given malaria and penicillin with satisfactory results had previously failed to be helped by either trivalent or pentavalent arsenotherapy. It is not possible to prove from this material that tryparsamide is a drug of little or no value. However, it is evident from this study that the *addition of tryparsamide* did not enhance the patient's opportunity for a successful outcome in terms of improvement in cerebrospinal fluid and/or relief of symptoms.

Discussion. Consideration of pharmacologic studies suggests that little value can be expected from tryparsamide as a therapeutic agent in the treatment of syphilis. The drug possesses very little spirocheticidal activity when compared to the trivalent arsenicals. Experimental data of Hogan and Eagle indicate that the arsenicals are only therapeutically effective in proportion to their ability to be bound by the parasite, and this activity depends on combination with essential sulfhydryl groups in the pathogenic organism. Since pentavalent arsenicals (as tryparsamide) are unable to unite with these physiologically active sulfhydryl groups until reduced to the trivalent forms (as arsenoxide), the rationale for the use of tryparsamide is open to question. Because more than half of the drug administered is excreted essentially unchanged in the urine within 6 hours, and between 80 and 90% within 24, there is little time for this reduction of the pentavalent form to the therapeutically active trivalent form. In contrast to the rapid rate that the pentavalent drugs diffuse through the kidney, the arsenoxide drugs (mapharsen, elorarsen, phenarsen) are retained by the patient. The optimum rate of excretion, according to Voegtlin and Thompson²² insures sufficient time for combination of drug and parasite, but not sufficient time to injure the tissues of the host. Moreover, no satisfactory evidence has been

advanced to justify the assumption that tryparsamide possesses greater penetrability or affinity for the central nervous system than the arsenicals of lower valency.

Except for its tendency to produce toxic amblyopia, tryparsamide is the least toxic of the arsenicals used in the treatment of syphilis. This finding is in keeping with the fundamental mechanism of the mode of action of chemotherapeutic agents as outlined by Ehrlich.⁸ He postulated that these agents are effective only if bound by the parasite, and the toxic activity is due to combination of the chemical agent to the tissues of the host. The number of cases of cutaneous, gastro-intestinal and nitritoid reactions caused by tryparsamide are small when compared to the minor and major reactions caused by the trivalent arsenicals. This absence of systemic toxicity suggests failure of tryparsamide to combine with the tissues of the host just as absence of therapeutic efficacy suggests failure of the pentavalent drug to combine with the parasite. In general, arsenicals are therapeutically active only to the degree that they are bound to the sulfhydryl group of the parasite and the host, and the differences in toxicity of these compounds is due to their varying affinity for tissues. Recently Hogan and Eagle¹¹ confirmed the postulation of Ehrlich by experimental studies. It is evident that what is considered therapeutically beneficial activity for the host represents toxic activity toward the parasite. This explains why both the toxicity of the pentavalent drugs (except of visual damage) and the therapeutic effects are of a low order.

In spite of the low toxicity of tryparsamide in terms of minor reactions, its tendency to induce damage to the optic nerves is great. In the series reported in this paper, 45% of all tabetics who received any tryparsamide experienced subjective and transient symptoms of optic nerve damage. In spite of apparently adequate precautionary measures, 20% of the tabetics progressed to permanent dam-

age characterized by disk pallor and restriction of visual fields. In all likelihood, this toxic manifestation of tryparsamide is not similar to the minor reactions, but represents a unique vulnerability of the optic nerve to the drug. The greater incidence of tryparsamide amblyopia in tabetics may be associated with subclinical damage to the optic pathways caused by syphilis.

It is difficult to evaluate the satisfactory results previously ascribed to tryparsamide. There are several factors which may be significant. Previous workers have found that good effects are obtained only by prolonged use of the drug, usually in conjunction with mercury and more recently with bismuth. It is likely that these benefits are dependent in part on the concurrent use of the heavy metal, in part on the activity of the trivalent arsenical which results from reduction of the pentavalent drug, and in part on the spontaneous changes that occur in cerebrospinal fluid with the passage of time. Another factor that handicaps interpretation in retrospect is the fact that, not uncommonly, patients were previously treated with agents of proved value such as trivalent arsenicals and malaria, but the good results were presumed due in whole or in part to tryparsamide.

Because the patients treated at the New York Hospital Clinic were so frequently given either concurrent or overlapping therapy, it is impossible from this study to prove that tryparsamide is an ineffec-

tive drug, but it is possible to show that it is not superior to the other antisyphilitic agents to which it is compared. It is possible to prove the effectiveness of both malaria and penicillin. Justification for the use of an agent such as tryparsamide which not infrequently causes partial or complete blindness would exist if no satisfactory alternative therapy were available and if proof of its therapeutic efficacy were irrefutable.

Summary and Conclusion. 1. Because pharmacologic studies show that pentavalent arsenicals, including tryparsamide, are not therapeutically effective until reduced to the trivalent form and do not possess greater penetrability or affinity for the central nervous system than the trivalent drugs, one cannot expect that tryparsamide will be an effective chemotherapeutic agent for the treatment of syphilis.

2. Tryparsamide often causes permanent visual damage in spite of detailed precautionary measures. This is especially true in patients with tabes dorsalis.

3. Considerable variation in the therapeutic results attributable to tryparsamide is evident throughout many reports. Patients with neurosyphilis treated in this clinic failed to substantiate the reported therapeutic efficacy of the drug.

4. There are alternative methods for treating all forms of neurosyphilis in which tryparsamide is said to be of value, and none of these regimens is as dangerous as one employing tryparsamide.

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RADIOLOGY

UNDER THE CHARGE OF

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THE MEDICAL USE OF RADIOACTIVE ISOTOPES

I. RADIOACTIVE ISOTOPES IN HEMATOLOGIC DISTURBANCES AND NEOPLASMS

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RADIOPHOSPHORUS. Radiophosphorus was the first radioactive isotope to be employed in the treatment of disease. Lawrence and his associates, as early as 1936, studied the possibilities of employment of this substance therapeutically in leukemia and allied diseases. Since then, the use of radiophosphorus as a therapeutic agent has been studied in a variety of conditions. Although the total number of patients treated with radiophosphorus is not large, sufficient time has elapsed to permit certain tentative conclusions to be drawn concerning the value and the limitations of this form of therapy.

Radiophosphorus (P^{32}) is prepared in the cyclotron by the bombardment, at high velocity, of ordinary red phosphorus (P^{31}) with deuterons (nuclei of heavy hydrogen). Neutrons are forced into the nuclei of some of the atoms, increasing the mass of such atoms by 1 (17 neutrons and 15 protons). Thus, the atomic weight of the new substance becomes 32. However, the number of protons and electrons in the atom is not changed, and since the chemical reactions of an atom are dependent on the number of electrons the atom contains, radiophosphorus behaves chemically in the same manner as does ordinary phosphorus. Consequently, when it is introduced into the living organism, radiophosphorus enters into all phases of phosphorus metabolism.

Radiophosphorus is unstable; it disintegrates at a constant rate through the emission of a beta ray. The emission of the beta ray occurs at the moment a neutron in the nucleus is changed to a proton. Although the mass of the new atom is not changed, the nucleus now contains 16 protons and 16 neutrons. Since the number of electrons equals the number of protons in an atom, a new substance chemically different from radiophosphorus is created. In this case, it is stable sulfur (S^{32}). Radiophosphorus does not emit alpha and gamma rays.

The rapidity of decay of any radioactive substance is expressed by the time required for half of an initial stock of atoms to disintegrate. This is called the "half-life" of the isotope. In the case of radiophosphorus, 35 of every 1,000,000 atoms undergo spontaneous transformation to stable sulfur each minute, giving radiophosphorus a half-life of 14.3 days.

The radioactivity of an isotope is measured in terms of millieuries. One millieurie (me.) is that amount of radioactivity produced by disintegration of 37,000,000 atoms per second. One microcurie (μ e.) is $\frac{1}{1000}$ of 1 me.

Radiophosphorus can be administered to patients, orally or intravenously, in the form of a phosphate. Usually, it is given in the form of monobasic or dibasic sodium phosphate. When the oral route is em-

ployed, from 15 to 50% of the amount administered is excreted in the urine and feces during the first 6 days¹⁰⁻²⁹. Most of this loss is caused by lack of absorption of the phosphate in the gastro-intestinal tract. As a general rule, it is safe to assume that 25% of the amount of radiophosphorus administered orally will be lost in the stool, and that 75% will be absorbed.

When radiophosphorus is administered intravenously to normal persons, from 25 to 50% of the quantity injected is excreted during the first 6 days. In leukemic and polycythemic patients, the excretion of the isotope is less than that which occurs in normal persons, varying from 5 to 25% of the amount injected over a similar period.¹⁰⁻²⁹ Thereafter, the rate of excretion in all persons falls to 1% or less per day. When the intravenous route of administration is employed, most of the loss occurs in the urine.

After administration, radiophosphorus is rapidly and selectively withdrawn from the blood by certain tissues and cells. According to Reinhard and his associates,²⁹ the selective uptake of phosphorus by cells is dependent principally on 3 factors: (1) the total amount of phosphorus in exchangeable form in the tissue, (2) the rate of turnover of phosphorus by the tissues and (3) the rate at which new tissue is formed.

As stated previously, in normal animals radiophosphorus is deposited in large amounts in bone and bone marrow, and in somewhat smaller quantities in the liver, spleen and lymph nodes. In the presence of pathologic conditions, the uptake of radiophosphorus has been found to be much higher in rapidly metabolizing neoplastic tissues than it is in the same type of tissue in a normal state of growth.

In leukemia and in polycythemia, the isotope is taken up rapidly by both circulating erythrocytes and leukocytes during the first 24 hours after the administration.^{2-11, 24} The concentration in the erythrocytes then decreases sharply, while the concentration in the leukocytes decreases

more slowly and the radiophosphorus is retained for much longer periods and in greater quantities than in the erythrocytes.

In certain diseases of the hematopoietic system, the distribution of radiophosphorus in various organs and tissues after it has been administered has received considerable attention.^{4-6, 20, 29, 33, 36} The studies of Reinhard and his associates²⁹ were especially illuminating in this regard. In chronic myelogenous leukemia, greater activity was found in the bone marrow than in any other organ, whereas in chronic lymphatic leukemia, the liver, spleen and lymph nodes in most instances contained a higher concentration of radiophosphorus than did the bone marrow. In acute leukemia or leukosarcoma, variable results were observed, but in general the liver and spleen accumulated more of the material than did the bone marrow. In most cases, however, the concentration of radiophosphorus was found to be lower in lymph nodes than in bone marrow, liver, spleen or kidney. In lymphosarcoma and actively progressing Hodgkin's disease, Erf and Lawrence⁸ found as great a retention of radiophosphorus in lymph nodes as in the liver and kidney. However, in 1 case of Hodgkin's disease in which the lymph nodes had become densely fibrotic, the uptake of radiophosphorus was lower than that in the other tissues assayed.

Data concerning the differential uptake of radiophosphorus in various organs in the presence of other diseases also have been accumulated. These diseases include melanoma and melanosis, seminoma, neuroblastoma, Ewing's sarcoma, fibrosarcoma, reticulum-cell sarcoma, multiple myeloma and metastatic carcinoma. In general, the distribution of the substance among different organs and tissues of the body depends on the type of neoplastic disease present, the degree of infiltration of an organ by abnormal cells and the rate of growth of these cells. Tissues which have a high concentration and a rapid turnover of stable phosphorus also take up higher concentrations of radiophosphorus than do normal tissues.

The depth of penetration of the beta rays emitted by radiophosphorus varies in different tissues, having a maximal range of penetration of approximately 7 mm.²⁹ The rays have the capacity to produce ionization in tissues, and therefore the radiation effects are basically similar to those of Roentgen rays and radium.

Because radiophosphorus is deposited predominantly in bone and bone marrow, the effect of the radiation produced by this agent is greater on the bone marrow than on other hematopoietic organs. Consequently, this form of therapy has been applied to diseases in which the bone marrow is involved primarily by a pathologic process, or to diseases in which the marrow is extensively involved, even though the primary site of the disease is in other organs. Since diseases of the blood fall into these 2 categories, the greatest therapeutic trial of radiophosphorus has been in the field of hematology. To date, radiophosphorus has seemed to be the treatment of choice in polycythemia vera.

POLYCYTHEMIA VERA. *Method of Treatment and Dosage.* For intravenous administration, a single injection of 3 to 7 mc. of radiophosphorus is given, the size of the dose depending on body weight, the age of the patient, and the severity of the disease. Approximately 25% of patients treated with radiophosphorus obtain satisfactory remission from a single injection.¹⁷ In patients in whom remission is not induced by the first injection, subsequent doses of 3 to 7 mc. may be injected at intervals of 8 to 12 weeks. The administration of radiophosphorus at intervals shorter than 8 weeks is inadvisable. Inasmuch as the life span of the erythrocyte of human beings has been shown to be 3 to 4 months, and since aged erythrocytes are removed slowly from the circulation, the degree of inhibitory action of the isotope on erythropoiesis cannot be assessed with reasonable accuracy in periods less than 8 weeks. Second or third injections of radiophosphorus can be carried out safely, provided that the erythrocyte count

has not fallen below 6,000,000 cells per c.mm. or the cell volume percentage below 55, and provided that marked suppression of the leukocyte or platelet levels has not occurred after the initial injection. If the erythrocyte count is less than 6,000,000 or the cell volume percentage is less than 55, further treatment with radiophosphorus should be withheld until a relapse occurs. If additional treatment with the isotope is indicated by the fact that the erythrocyte count remains above 6,000,000 or the cell volume % remains above 55, and if a marked decrease in the number of leukocytes or platelets occurred after the first injection, then smaller doses than were employed in the first instance should be given.

Because a decrease in erythrocyte, hemoglobin and hematocrit values does not occur, as a rule, within less than 6 to 8 weeks after the initial injection of the isotope, and since patients who have uncontrolled polycythemia vera run an increased risk of thrombosis, some observers^{17,18} recommend that venesection be performed repeatedly prior to the initial injection of radiophosphorus.

Results. Since Lawrence²⁴ first reported the successful treatment of 2 patients who had polycythemia vera with radiophosphorus, the results of treatment in 273 cases have been reported.^{3,7,14,17,18,24,25,35} Detailed follow-up data have been published by Reinhard and associates²⁹ and by ourselves¹⁷ in 84 cases. Satisfactory hematologic remission was obtained in approximately 85% of the 84 cases; partial remission was induced in the remaining 15%. A decrease in values for leukocytes and platelets preceding or accompanying the decrease in erythrocytes also occurred in the majority of cases. Subjective improvement occurred in cases in which a substantial decrease in values for erythrocytes and a reduction in blood volume were noted. In many cases, the degree of symptomatic relief was pronounced, resulting in restoration of a sense of normal well-being. Except in occasional cases of long-standing disease

in which the spleen had become enormously enlarged, firm and presumably fibrotic, treatment resulted in reduction in the size of this organ, often to the point at which it no longer could be palpated. Generally, when hepatomegaly was present, some reduction in the size of the liver occurred. Other objective signs, such as ruddy cyanosis, conjunctival injection and distention of retinal venules also either abated or disappeared.

Sufficient time after the institution of radiophosphorus therapy in polycythemia vera has not elapsed to permit a definite analysis of the duration of the remission induced with this form of treatment. However, Reinhard and associates,²⁹ Erf³ and ourselves¹⁷ reported comparable results with remission which endured 5 months to 4½ years. Among the 84 patients treated by Reinhard and by ourselves, 62 obtained remission which lasted more than 6 months, 25 obtained remission which lasted more than 1 year, and 10 obtained remission which lasted more than 2 years. However, the disease of many of these patients was still in remission at the time the reports were published, so that further observation over a prolonged period will be necessary to determine how long remission will last. When polycythemia vera recurs, remission can be induced a second time by the administration of more radiophosphorus.^{3,17,29}

Whether or not radiophosphorus therapy significantly prolongs the lives of patients who have polycythemia vera has not been determined. Detailed data on the duration of life in a large series of patients, either untreated or treated by means of venesection, the administration of phenylhydrazine or Roentgen radiation, are not available. However, in 36 of 163 cases of polycythemia vera in which follow-up data could be obtained, Tinney, Giffin and 1 of us (Hall)³⁰ reported on 32 who lived more than 5 years after the diagnosis had been established, 28 who lived more than 10 years, 8 more than 15 years, and 4 more than 20 years. Two patients living 5 years after the diagnosis

had been made had not been treated; all others had received treatment of some kind, although in many instances treatment had been inadequate or had been discontinued voluntarily by the patient. The course of the disease, therefore, is chronic and often of long duration. Death most commonly results from vascular complications (coronary or cerebral thrombosis or pulmonary embolism), hemorrhage, intercurrent infection, or a terminal "leukemic" blood picture associated with anemia. Erf³ recently published data on the causes of death among 214 patients who had polycythemia and who had been treated with radiophosphorus at various institutions in this country. Thirteen deaths were recorded, 5 in which the terminal blood picture was indistinguishable from that of myelogenous leukemia; 3 in which there were malignant tumors; 3 in which there was intercurrent infection; 1 in which there was hypoplastic anemia and 1 in which there was gastric hemorrhage. The absence of venous thrombosis as a cause of death in the aforementioned group would appear to be significant. Data concerning 102 additional patients with polycythemia vera treated with radiophosphorus, not included in Erf's report, have shown acute leukemia to be the cause of death in 2, congestive heart failure in 1, and probable coronary thrombosis in 1.¹⁶ Acute leukemia, therefore, has been the principal cause of death among polycythemic patients treated with radiophosphorus to date. The incidence of leukemia in the treated group is 2.2% (7 of 316 cases), but this figure is well below the percentage of 10 as reported by Tinney and associates³¹ as dying with a blood picture indistinguishable from that of chronic myelogenous leukemia in a series of 163 cases of polycythemia vera studied prior to the institution of radiophosphorus therapy. Since a longer period of time may increase the incidence of acute leukemia, eventually this may prove to be a less valuable form of treatment than it appears at present.

Complications. The complications encountered when this form of therapy is used are largely hematologic, in the form of thrombocytopenia, leukopenia and anemia. These complications are comparatively common. Among the 54 cases in our series, leukopenia developed in 54%, thrombocytopenia in 39% and anemia in 18%. Any one of them was found to occur singly or in combination with one of the others, but in only 1 case were thrombocytopenia, leukopenia and anemia observed simultaneously.

Considerable variation in the period of time elapsing between the administration of the isotope and the development of the complication was noted. Leukopenia developed within 2 weeks to 6 months after the injection of radiophosphorus, thrombocytopenia within 3 weeks to 2 months, and anemia within 2 to 10 months. The anemia and leukopenia were of relatively short duration, and no complications were noted as a result of their development. The thrombocytopenia, when it developed, tended to last somewhat longer, extending over periods of 4 to 8 weeks. The only hemorrhagic phenomenon observed was the development of petechiae on the extremities in 2 cases. No deaths as a result of the aforementioned complications have been reported.

LEUKEMIA. Administration of radiophosphorus in leukemia and allied diseases differs from that in polycythemia vera. An attempt is made to minimize the inhibitory effect of the isotope on the formation of erythrocytes and blood platelets while, at the same time, a maximal depressant effect on leukopoiesis is being obtained. This can be accomplished by the administration of radiophosphorus twice a week according to the "fractional method" of Low-Beer, Lawrence and Stone,²⁶ until the desired result has been obtained. An initial dose of 1 to 3 mc. usually is administered. Thereafter, the size of the biweekly injections varies from 0.5 to 2 mc. Treatment must be highly individualized because of the great varia-

tion in response shown by the different patients.

Reports on the use of radiophosphorus as a therapeutic agent have been published concerning 136 patients with chronic or subacute myelogenous leukemia,^{2,12,14,17,20,25,29} 98 patients with chronic or subacute lymphatic leukemia^{2,12-14,17,20,24-26,29,35,37} and 109 patients with various types of acute leukemia.^{2,12,17,20,22,23,26,29,35,37} Significant beneficial results have not been observed in any of the cases of acute leukemia. In the chronic forms of the disease, results comparable to those secured with Roentgen radiation have been obtained. Clinical and hematologic remission has been induced in a high proportion of patients, but published reports do not indicate that the duration, either of individual remission or of life, is greater than that noted after Roentgen ray therapy.

The results of treatment in chronic myelogenous leukemia appear to be somewhat better than those obtained in chronic lymphatic leukemia.^{12,29} A progressive decrease in leukocyte values, often accompanied by an increase in values for hemoglobin and erythrocytes, reduction in the size of the spleen and liver, and symptomatic improvement, occurs in most patients, except those in the terminal stage of the disease.

In chronic lymphatic leukemia, the number of patients who obtain satisfactory remission is somewhat lower than it is in chronic myelogenous leukemia. Although a reduction in the leukocyte count and improvement in the blood picture are observed in a significant proportion of patients, less recession of the patient's symptoms and anemia occurs. Some reduction in the size of lymph nodes and of the spleen commonly is observed, but in most cases it also appears to be less than that obtained by Roentgen ray radiation.

On the basis of data collected by various observers, the administration of radiophosphorus in the chronic leukemias has been found to bring about hematologic remission and clinical improvement in a

manner comparable with that obtained with Roentgen ray therapy. However, the use of this isotope does not cure the disease. The chief advantages of this form of treatment are the ease of administration and the absence of radiation sickness. The principal disadvantages are the greater length of time required to bring about the desired therapeutic result and the greater risk of injury to the bone marrow, especially with regard to inhibition of the formation of blood platelets to the point at which serious hemorrhagic complications might develop. In carefully selected cases, once remission has been induced by means of Roentgen ray radiation, radiophosphorus has been found to be effective in holding leukocyte counts at or near normal levels for long periods.^{16,17} Used in this way, radiophosphorus therapy eventually may prove to be a useful adjunct to treatment with Roentgen rays.

MISCELLANEOUS DISEASES. From the results thus far reported, radiophosphorus therapy does not appear to be as effective as Roentgen ray radiation in Hodgkin's disease, lymphosarcoma or reticulum-cell sarcoma.^{14,17,19-21,26,29,35} In myeloma it does not inhibit progression of the disease, although pain in the bones may be relieved in a high proportion of cases.^{12,14,17,29,26,29,35} In osteogenic sarcoma, malignant melanoma, carcinoma of the gall bladder, disseminated carcinoma of the breast, lympho-epithelioma, mycosis fungoides and xanthomatosis, radiophosphorus is not a satisfactory therapeutic agent.^{14,20,29}

Summary of Radiophosphorus Section. In summary, on the basis of present evidence, radiophosphorus therapy provides an effective means for the control of polycythemia vera. Remission, often of long duration, can be induced in a high proportion of cases. The chief advantages of this form of treatment appear to be the ease of administration, the absence of radiation sickness and symptoms of toxicity and the simplicity with which the dose can be controlled. The principal disadvantages are the cost of the material and

the fact that the bone marrow may be injured seriously in the case of overdosage or an unusual sensitivity of the marrow to therapeutic doses. Moreover, the possibility that radiophosphorus may cause terminal acute leukemia must be borne in mind. In the chronic leukemias, radiophosphorus induces remission similar to that produced with Roentgen rays, but therapy with this isotope apparently has no particular advantage over the latter form of treatment and requires a longer period to bring about the desired result. In multiple myeloma, radiophosphorus relieves pain in bones in a significant proportion of cases, but does not inhibit the systemic progression of the disease. In the lymphomas, radiophosphorus therapy appears to be less effective than Roentgen ray treatment, and in acute leukemia, metastatic tumors, mycosis fungoides and xanthomatosis, the isotope is ineffective as a therapeutic agent.

RADIOSTRONTIUM. Although the most extensive studies of radioactive elements in the experimental laboratory and in the human being have been carried out with radiophosphorus, other radioactive elements have been produced and the use of them in both animals and human beings has been investigated. Since radiostrontium is picked up readily by growing bone, use of it in animals and human beings has been investigated; but because of its half-life of 180 days and its weak available activity, its therapeutic use has been slight.

The similarity between calcium and strontium led Pecheur²⁵ to investigation of radiostrontium (S^{90}) which has a half-life of 55 days and emits beta rays similar to those of radiophosphorus. It has been found that the dose of radiation afforded by radiostrontium is highest in the regions in which an osteoplastic process exists, as in osteogenic sarcoma and the osteoplastic metastasis of carcinoma of the prostate gland.

Radio-strontium lactate is readily concentrated in growing bony tissue. Tread-

well and associates³² found that the high uptake of strontium occurs in areas in which new bone is being laid down, whether the new bone is normal or neoplastic. They felt that radiostrontium would constitute a valuable tool in the study of the healing of bone after experimental fractures.

RADIO-IRON. Radio-iron employed as a tracer substance has proved of value in the study of iron metabolism and the formation and destruction of the blood. When tracer doses of radio-iron are used, a group of iron atoms can be traced throughout the body by means of a Geiger-Müller counter. Since the material used in tracer doses is without danger to human beings, this material can be used safely in both normal persons and persons who have various blood dyscrasias.

Many very interesting studies have been carried out in an attempt to explain the absorption of iron. It has been shown that iron is absorbed by the body only when it is needed to replace depleted iron reserves.

Radio-iron has been used to determine the true erythrocyte cell volume of the blood, which was found to be approximately 8.5% lower than the centrifuge hematocrit volume.¹

Peacock and associates,²⁷ using 2 radioactive isotopes of iron, F^{59} , with a 47 day half-life, and F^{55} , with a 5 year half-life, have carried out tracer studies and have presented methods of utilization of these substances in experimental medicine.

Gibson and associates¹⁵ published a method of determination of the circulating erythrocyte volume by the use of 2 radioactive isotopes of iron. This method gives an absolute measure of the circulating erythrocyte, a measure which is independent of the venous, arterial or auricular hematocrit reading. The method has been applied to the study of normal erythrocyte cell volume as well as experimental shock, arterial occlusion, burns and bacillary toxins.

RADIOSODIUM. One isotope of radio-sodium, which has a half-life of 14.8 hours, has been used in the treatment of leukemia. This material distributes itself throughout the extracellular and intracellular fluid, and maintains a nearly constant level of radiation in the blood stream. It emits beta rays and hard gamma rays, and therefore acts very much like spray Roentgen therapy, with uniform radiation of the body.

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RADIOLOGY

UNDER THE CHARGE OF

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THE MEDICAL USE OF RADIOACTIVE ISOTOPES

II. RADIO-IODINE AND THE THYROID

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BECAUSE of the specific affinity of the thyroid for iodine and the specific rôle of iodine in the formation of thyroid hormone, it is not surprising that radio-iodine has been applied promptly and widely to the study of problems in thyroid physiology and thyroid disease. At least 8 different radioactive isotopes of iodine have been described and at least 4 of these have been used in biologic investigations.¹⁵ However, I^{131} (half-life, 8 days)* and I^{130} (half-life, 12.6 hours) or a mixture of both have been utilized in most investigations. Both of the isotopes give off relatively strong beta rays and relatively feeble gamma rays. They are prepared by bombardment of tellurium with neutrons in the cyclotron. Much of the radio-iodine which has become available to medical investigators was prepared in the cyclotrons of the Massachusetts Insti-

tute of Technology and the University of California. Without the excellent collaboration and coöperation of the staffs of these and other laboratories, this field could not have developed so rapidly.

PHYSIOLOGIC APPLICATIONS. Hertz¹¹ in 1937 was first to investigate the possibilities of radio-iodine as an indicator in thyroid physiology. He used the tracer technique.†

Hertz¹² and many other subsequent investigators found that the thyroid collected iodine with avidity and that the degree of such avidity for iodine could be correlated with various histologic and physiologic states of the thyroid. Iodine deficiency, administration of potassium thiocyanate,¹³ and soy bean diet all increased the affinity of the thyroid for iodine.¹² The previous administration of iodine or of thyroxin and hypophysectomy

* I^{131} designates iodine with atomic mass of 131 to distinguish it from natural iodine (mass, 127). By "half-life" is meant the time required for half of any quantity of the isotope to disappear.

† "Tracer technique" refers to the use of radioactivity to trace the course of minute quantities of material through various reactions. The chief value of such methods lies in their application to the study of metabolic processes under conditions of physiologic equilibrium. Many problems, especially those involving rates of collection and turnover, can be approached now for the first time by means of this technique.

were among the factors which reduced it. Thiouracil and related goitrogenic substances promptly and markedly decreased iodine collection before any other effects of these agents were evident.¹⁹ Chaikoff and his associates^{2,17} have used radio-iodine in *in vivo* and in *in vitro* studies to examine the rate and mode of formation of diiodotyrosine and thyroxine. Other studies have dealt with the mode of action of thyrotropic hormone, qualitative differences in the action of various goitrogens, functional maturation of embryonal thyroid tissue and numerous related problems.

CLINICAL INVESTIGATIONS. While its use in studies involving experimental animals has been productive, radio-iodine offers its greatest promise in the investigation of thyroid function in man. Hamilton and Soley⁵ were the first to study the behavior of radio-iodine in man. Hertz and his colleagues,⁸ Rawson¹⁸ and others also have explored the method extensively. Radio-iodine is collected by the thyroid in substantial amounts. Most of the iodine not collected by the thyroid is excreted in the urine; only insignificant amounts appear in the feces. Euthyroid persons excrete up to 80% of a given dose in the urine; myxedematous patients, up to 95%, and persons who have untreated thyrotoxicosis, a much smaller percentage than those who have normal thyroids.⁶

Hamilton and Soley⁶ have measured directly the collection of iodine in the thyroid by placing a Geiger-Müller counter over the thyroid. They found that both the collection of iodine by the gland and the subsequent disappearance from the gland can be followed in this way. Despite its technical limitations, this procedure offers great promise. When it can be supplemented by an accurate method for measuring radio-iodine in blood in addition to the measurement of urinary excretion, it will be possible to examine more precisely than heretofore the altered

dynamics of iodine metabolism in thyroid disease.

Hamilton and Soley⁷ have also pioneered in applying the technique of autoradiography* to the study of surgically removed thyroid tissue. By this means they and others investigated the microscopic distribution of radio-iodine in the thyroid and were thus able to correlate the structure of the gland with the distribution of iodine.

The application of tracers of radio-iodine to the study of patients is somewhat limited by the necessity of avoiding doses of radiation which are sufficient to modify thyroid function because of 2 factors: (1) the risk of producing artefacts which may be misinterpreted, and (2) the hazard of exposing the thyroid to undesirable quantities of radiation. All of the tracer studies reported so far involve quantities of radiation in the thyroid which substantially exceed the arbitrary tolerance dose of 0.1 r per day, a dose generally accepted as permissible in work with Roentgen rays and radium.

Radio-iodine probably will find its chief use as a tool for the study of thyroid function. However, it also has some promise as a therapeutic agent. Hertz and Roberts⁹ in 1942 reported preliminary observations made in 10 cases of exophthalmic goiter treated with radio-iodine. Hamilton, Lawrence and Soley^{4,5} also reported early results with the treatment of exophthalmic goiter. While both groups were encouraged by their trials, they did not publish sufficient detail for an adequate appraisal of the procedure. Hertz and Roberts¹⁰ recently have reported a detailed follow-up study of their experience in treating 29 patients, and Chapman and Evans¹ have published similar data concerning an additional series of 22 cases. Remission of hyperthyroidism was observed in a majority of cases in both series. In the group of patients treated by Chapman and Evans the average dose of radia-

* An autoradiograph is made by applying a sensitized emulsion to a thin microscopic section of thyroid tissue, which previously had collected radio-iodine, for a sufficient time to allow the radiation from the radio-iodine to expose the emulsion. The resulting pattern discloses the distribution and density of the radio-iodine in the tissue.

tion given was 2 to 3 times as much as that used by Hertz and Roberts. Of the 22 patients in Chapman and Evans' report, 20 were relieved of hyperthyroidism; in 4 of the 20 cases myxedema developed. Mild reactions resembling radiation sickness occurred in 6 cases.

So far, it appears that the possibilities of treating thyroid cancer with radioiodine are very limited. As Hamilton was first to point out,⁷ lack of success is due to the fact that most malignant lesions of the thyroid are unable to collect or store iodine. However, 3 cases have been reported in which thyroid carcinoma and distant metastatic lesions collected radioiodine in amounts sufficient for treatment.^{3,14} In 1 case prolonged treatment with radioiodine effected a remarkable arrest of widespread bony metastatic lesions.²⁰ It is reasonable to assume, therefore, that a few malignant lesions of the thyroid actually will prove amenable to this form of treatment. Even though, as seems probable, such cases prove to be a very small proportion of thyroid malignancies, treatment with radioiodine is sufficiently promising to justify a careful search for cases in which it might be effective.

The therapeutic application of radioiodine is complicated by the difficulties of determining the dose of radiation received. Various aspects of this highly technical subject have been discussed by Marinelli¹⁶ and by Chapman and Evans.¹ The biologic factors which must be known and measured in order to determine dosage include the actual weight of the thyroid gland, the quantity of a given dose collected by the thyroid and the rate at which iodine is excreted subsequently by the thyroid. The purely physical factors

include the qualitative character and specific energy of the radiation of the isotope employed, as well as the half-life of the isotope. Most of the foregoing can be determined, at least approximately, but other variables cannot. These variables include variations in radiosensitivity due to varying degrees of hyperplasia or the like. On this account it seems likely that, for the present at least, dosimetry may remain on a somewhat empiric basis.

In all therapeutic studies reported thus far a mixture of radioactive isotopes of iodine consisting chiefly of I^{130} has been employed. Because of the physical limitations of the cyclotron this could be prepared only in relatively small quantities and because of its short half-life it was useful only to investigators within the immediate vicinity. In recent months, I^{131} prepared in the uranium piles of the Clinton Laboratories has become available in large quantities, and consequently it is now receiving extensive therapeutic trial. Since the physical characteristics of I^{131} are different from those of I^{130} , the problem of effective dosage is certain to be different.

It must not be thought that use of radioiodine, either as a tool for investigation or as a therapeutic agent, is without danger. The handling of radioiodine requires the same kind of precautions against the insidious and disastrous consequences of radiation for the patient, the physician and the technician as does the use of radium or Roentgen rays. This is particularly the case because of the penetrating character of the gamma rays. Much more information is needed concerning minimal quantities which are capable of producing radiation effects both on the thyroid gland and other organs.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MARCH 18, 1947

Hepatic Purine Nitrogen Partition in Normal and Injured Rats. By JULIUS SCHULTZ and HARRY M. VARS (Harrison Dept. of Surg. Research, Univ. of Penna.). To obtain a clearer understanding of the mechanism by which a sterile abscess affords protection against hepatic damage due to chloroform anesthesia¹, the composition of the liver under these circumstances was investigated. The purine-N and total heat-coagulable protein (Addis) of the livers of 24 and 48 hour fasted rats pooled in groups of 5 were compared with values obtained from comparable groups abscessed, anesthetized or receiving both treatments.² All animals had received a stock diet plus 12% casein for 2 weeks prior to the experiments.

thetia and 3.9 with anesthesia. Anesthesia alone resulted in a ratio of 3.9.

A partition of the total purine-N into nucleotide, nucleoside, free and protein-bound purine was made. The increased levels of purine-N were due chiefly to the purine-N of the protein.

The nucleic acid content of the heat-coagulable protein was calculated from the purine-N and phosphorus contents of the protein. By subtracting this value from the total protein the quantity of the nucleic-acid-free protein was determined. The data have been expressed as the quantities present per liver of a 200 gm. rat. The increments of protein and nucleic acid of the injured animals over the amounts found in the 48 hour fasted con-

TABLE 1.—PROTEIN AND NUCLEIC ACID CONTENT OF THE LIVER OF THE 200 GM. RAT EXPRESSED AS INCREMENTS ABOVE THE BASAL VALUES OF ANIMALS FASTED 48 HOURS

Treatment	Groups no.	Fast hrs.	Protein (A) mg.	Nucleic acid (B) mg.	(A)/(B) × 100
Basal level	3	48	1145	67	5.8
<i>Increments of Groups</i>					
Fed	3	0	479	15	3.1
Fasted	3	24	183	—2	0.0
Abscessed	2	24	256	16	6.2
Anesthetized	3	24	255	3	1.2
Anesthetized	2	48	30	2	6.0
Abscessed—anesthetized	3	24	236	15	6.4
Abscessed—anesthetized	2	48	90	6	6.7

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Increased quantities of purine-N and protein were found in the livers of the injured rats. The ratios of (purine-N to total nitrogen) × 100 were significantly greater in these animals than in the fasted or fed controls. The fed and fasted rats showed a ratio of 3.6 while the abscessed animals had ratios of 4.2 without anes-

thetia. The nucleic acid composition of this increment was greater in the abscessed animals, with and without anesthesia, than in the fed or 24 hour fasted rats. These changes are characteristic of the relationships observed in tissues actively forming new protein.

Calcium Binding Property of the Serum Proteins. By A. J. RAWSON, M.D., and F. WILLIAM SUNDERMAN, M.D. (Pepper Laboratory, Hosp. of the Univ. of Penna.). After separating the serum proteins by means of methanol precipitation of the globulins it is possible to measure the calcium binding property of both the albumin and total globulins without resorting to the isolation and purification of these fractions. In normal sera the average value of calcium bound to albumin was found to be 0.95 (s.e. = 0.04) mg. of calcium per gm. of albumin, and that of calcium bound to globulin, 0.74 (s.e. = 0.03) mg. of calcium per gm. of globulin.

The calcium binding property of the protein fractions was studied in sera obtained from patients suffering from multiple myeloma, lymphogranuloma venereum and sarcoidosis. It was found that in the sera of 9 out of 10 patients studied the value of the calcium binding property of albumin was increased to as much as 6 times the normal. The evidence suggests that an altered form of albumin may appear in the albumin fraction in these diseased states. It was also observed in these conditions that the value of the calcium binding property of the total serum globulins varied from the normal, and appeared to be dependent upon the predominating type of globulin present.

The hypercalcemia present in 2 of our cases of multiple myeloma was due to an increased concentration of calcium bound to protein. This increase was dependent upon 2 factors: (a) the increased binding power of the serum albumin, and (b) the increased concentrations of total globulins, with approximately normal binding property.

Pulmonary Artery Pressure in Phosgene Poisoning. By MARY GIBBON, H. D. BRUNER, M.D., R. D. BOCHE, Ph.D., and J. S. LOCKWOOD, M.D. (Harrison Dept. of Surg. Research, Univ. of Penna.). In order to decide whether the pulmonary edema of phosgene poisoning was due primarily to toxic endothelial damage or

to elevated hydrostatic pressure, the pressures in the lesser circulation were measured in 5 cats following exposure to phosgene. The marsupialized heart preparation avoided the necessity of anesthesia and thoracotomy; the pressures were procured by means of specially designed air-damped manometers. In favorable preparations, the right and left atrial pressures also were measured. No evidence of raised pulmonary artery, pulmonary vein or systemic venous pressure was observed. Immediately after exposure to potentially lethal doses of phosgene, pulmonary artery and systemic arterial pressure decreased while the atrial and venous pressures remained approximately unchanged or were slightly lower; terminally all pressures tended to return toward pre-gassing levels. The operation may have facilitated development of pulmonary congestion, but these cats behaved in all respects like simultaneously gassed controls, and at autopsy their lungs were typical of phosgene poisoning.

These data exclude abnormal hemodynamics as a cause of the increased permeability of pulmonary capillaries in phosgene poisoning. Therefore, despite our inability to find histologic evidence of endothelial damage, we must postulate that such damage is present; collateral evidence supports this view.

The Effect of Carbon Dioxide on the Initial Ventricular Deflection of the EKG. By THOMAS DURANT, M.D., JOAN LONG, M.D., M. J. OPPENHEIMER, M.D. (Depts. of Physiology and Medicine, Temple Univ. Medical School). In the course of studying experimental air embolism,¹ the action of intravenous carbon dioxide on the EKG of the dog was investigated. Direct leads were taken from the anterior surface of the right ventricle in open chest experiments with dogs under nembutal anesthesia. When 50 cc. of CO₂ are rapidly injected into a femoral vein, the initial upward deflection is decreased in amplitude or disappears entirely in the direct

lead from the right ventricle. The S wave is slightly increased and the S-T segment is raised. The gas quickly disappears from the right ventricle (15 to 17 seconds) and the EKG returns to normal within 1 to 3 minutes. The decrease in amplitude of R is proportional to the amount of CO₂ injected. In the limb leads, the reduction of R is most pronounced in Lead 3. When 30 cc. of 1% procaine is injected the QRS interval (duration) is increased, and when the action of CO₂ is superimposed on that of procaine, the pattern from the surface

of the right ventricle resembles that of right bundle branch block.

These changes are not due to dilatation of the right ventricle, as air causes greater dilatation but no change in R. The change occurs when both the sympathetic and the vagi are cut. The injection of 0.1 N HCl did not cause a lowering of R. The change failed to occur at a pH of 7.4 at one time and did occur at the same pH at another. The question is raised as to whether this change could be due to the specific action of CO₂ on the cardiac conduction system.

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BOOK REVIEWS AND NOTICES

ESSENTIALS OF CLINICAL PROCTOLOGY. By G. SPIESMAN, B.S., M.D., Proctologist, Mt. Sinai and Edgewater Hospitals; Consulting Proctologist, Grant, Henrotin and St. Elizabeth Hospitals. Pp. 238. New York: Grune & Stratton, 1946. Price, \$4.00.

THE Reviewer has been somewhat at a loss in reading this little book to determine to what group of readers it is addressed. The description of the anatomy of the anorectal region is surely for students of medicine, but reference to "pain pills" and to the dosage of sulfadiazine and sulfauxidine in terms of the number of "tablets" to be given is surely for others than students.

The author discusses the various proctologic conditions from a practical point of view and in addition adds lists of symptoms and differential diagnosis in tabulated form.

The Reviewer cannot conscientiously say that this volume adds to our knowledge of clinical proctology, but it is possible that it may be of use to a beginning general practitioner who will meet in his practice some of the conditions here discussed. I. R.

HOSPITAL CARE OF THE SURGICAL PATIENT.

By GEORGE CRILE, JR., M.D., Surgeon, Cleveland Clinic, and FRANKLIN L. SHIVELY, JR., M.D., Assistant Surgeon, Cleveland Clinic. 2nd ed. Pp. 288. Springfield, Ill.: Charles C Thomas, 1946. Price, \$3.50.

THE demand for the 1st edition of this handbook has made a 2nd edition necessary within 3 years. The authors state that this is not a reference book, but it is more than likely that surgical interns and residents will find it useful as such, as well as for the purpose for which it was intended—that is, to introduce the surgical house staff to the more common procedures in modern surgical care.

It is refreshing to find in the discussion of surgical complications that the cause of the complication is always emphasized so that the young surgeon will be alert to forestall the development of such complications whenever possible.

The Reviewer recommends this handbook to all surgical residents and to the general surgeon as well. I. R.

THE TRAUMATIC DEFORMITIES AND DISABILITIES OF THE UPPER EXTREMITY. By ARTHUR STEINDLER, M.D., F.A.C.S., Professor and Head of the Department of Orthopedic Surgery, The State University of Iowa. In collaboration with JOHN LOUIS MARXER, M.D., Associate, Orthopedic Department, State University of Iowa. Pp. 515; 1048 ills. Springfield, Ill.: Charles C Thomas, 1946. Price, \$10.00.

DR. STEINDLER's book appears at an opportune time and should prove a valuable guide to the numerous members of the medical profession concerned with the problems of reconstructive surgery which have arisen from World War II. It deals with the delayed results of trauma rather than the initial care of injury. The first part of the book, "General Considerations Pertaining to Traumatic Disabilities of the Upper Extremity," is largely introductory in character and concerns principles applicable almost as much to the lower as to the upper extremities, although mobility is stressed throughout as the predominant requirement for the arm in contrast to stability for the leg. This introductory section emphasizes the close interrelationship of the joints of the extremity and the fact that all joints must be subservient to the proper functioning of the hand. Without this overall picture it is difficult to plan correctly the proper reconstructive procedures.

The second and major part of the book is presented in the form of "case histories" rather than as a text, with special emphasis on clinical and diagnostic features. For this reason it will be exceptionally useful in the handling of individual cases.

Operations for the habitual dislocation of the shoulder joint are discussed at length. The author favors the Nicola and Henderson operations. For unreduced fracture dislocations of the neck of the humerus he advises open reduction or resection. Resection is used in the majority of older injuries al-

though many do not require operation if pain is not an important factor. The massive onlay bone graft is preferred for non-union of the humerus, radius and ulna. The bone is taken from the tibia and fixed with vitalium screws.

Disabilities of the elbow are grouped from the physiologic and functional point of view rather than the anatomical. Cubitus varus and valgus, intra-articular blockage of the elbow, extra-articular contractures, intra-articular adhesions, disabilities following unreduced dislocation, traumatic arthritis, and nerve palsies are presented along with the indicated operations and case reports.

The controversial question of the proper operative treatment of non-union of the scaphoid is answered by giving the following choice of operations with the special indications for each: drilling of the bone, bone graft and resection of the scaphoid.

In the discussion of the deformities of the hand the work of Bunnell is quoted frequently. The use of bone grafts taken from the crest of the ilium and fixed with wires or pins through the medulla is not mentioned. This method, which has been used extensively in Army orthopedic centers for non-union of the metacarpals, has proved to be valuable.

This volume is the work of an authority, excellently written, and supplemented with clear and appropriate illustrations.

W. F., Jr.

SPEZIELLE CHIRURGISCHE THERAPIE. By DR. MAX SAEGER-SEIL, Privatdozent für Chirurgie, Bern. Pp. 884; 1989 ill. Bern: Hans Huber, 1946. Price, \$20.00.

This volume is one of a group of medical handbooks for doctors and students published by Huber. The author has set as his aim the answer to 2 questions: What is the best thing to do in a certain surgical situation and how is this best done? The answers to these questions are definitely and clearly stated in the text. The entire range of surgery from traumatic neurosurgery to fractures and other diseases of the extremities is covered in detail with frequent illustrations to permit the reader to follow easily the anatomy and the steps of the operative procedure presented. The detail that is given is much greater than would be com-

monly found in American textbooks. Every step of the diagnosis and of the operative procedure is described and the postoperative care is written to include all the usual postoperative orders for each day. The various possible postoperative complications are described for each disease separately.

The book lacks a section on anesthesia, and the modern emphasis on nutrition of the surgical patient is not found in the description of the postoperative care. In the section on fractures, the treatments prescribed are similar to those of Boehler.

On the whole, the book is well written. The illustrations are pen and ink drawings that show well what the author wishes to illustrate.

L. F.

PULMONARY EDEMA AND INFLAMMATION.

By CECIL K. DRINKER, M.D., D.Sc., Professor of Physiology, School of Public Health, Harvard University. Pp. 106; 27 figs. Cambridge, Mass.: Harvard Univ. Press, 1945. Price, \$2.50.

This Harvard University Monograph in Medicine and Public Health includes a series of 4 lectures by the author in which the processes involved in the formation and removal of pulmonary transudates and exudates are analyzed. A fifth chapter upon artificial respiration has been added.

Few authors write in as clear and entertaining a fashion as does Dr. Drinker. In this monograph he has presented a potentially difficult subject so masterfully that even a physician only mildly interested in the subject will read it as easily as a novel. Much of the experimental work reported in this book has been carried out by Dr. Drinker and his associates and he recounts this work as a series of adventures in pulmonary physiology. It is indeed refreshing to turn to this type of presentation and it is hoped that more authors will present their investigations in such personal form.

J. C., Jr.

TECHNIQUE OF PSYCHOANALYTIC THERAPY.

By SANDOR LORAND, M.D., Member of the Faculty of the New York Psychoanalytic Institute. Pp. 251. New York: International Univ. Press, 1946. Price, \$1.50.

In this volume the author presents material used in an advanced seminar and colloquium in technique at the New York Psychiatric Institute. The book presumes in

the reader some knowledge of basic psycho-analytical theory and is meant primarily for the psychoanalyst in training. The author stresses flexibility in technique and interpretation and refreshingly states that at times the therapist must be satisfied with practical results which enable the patient to get along better than he did prior to therapy.

The author uses partial case histories to illustrate problems in technique. Partial contents: Anxieties and Phobias; Sexual Difficulties; Compulsion Neuroses; Dream Analysis; Counter Transference, Termination.

J. W.

X-RAYS AND RADIUM IN THE TREATMENT OF DISEASES OF THE SKIN. Edited by GEORGE M. MACKEE, M.D., Professor of Clinical Dermatology and Director, Dept. of Dermatology, New York Post-Graduate Med. School and Hospital, Columbia Univ., and ANTHONY C. CIPOLLARO, M.D., Assistant Professor of Dermatology and Assistant Director, Dept. of Dermatology, New York Post-Graduate Medical School and Hospital, Columbia Univ. Contributor: HAMILTON MONTGOMERY, M.D., Associate Professor of Dermatology, Mayo Foundation, Univ. of Minnesota. 4th ed. Pp. 668; 325 ills. Phila.: Lea & Febiger, 1946. Price, \$10.00.

THIS book has fulfilled over the years a demand of radiologists and dermatologists. The historical, engineering and physical considerations of roentgenology and radium are beautifully done by Dr. Edith Quimby. Every radiologist should be thoroughly familiar with the fundamental considerations of radiation therapy, which are beautifully described and illustrated in the text. The biologic and biochemical considerations of irradiation, also considered by Dr. Quimby, are also well done. Dr. Montgomery's chapter on the pathologic histology of radio-dermatitis is excellently prepared and gives important information.

The Reviewer obtains the impression that the factors recommended in the treatment of various lesions under "therapeutic considerations" need to be amplified in order that the inexperienced dermatologist may use this book as a guide. Factors that are used in treatment should be described carefully. The necessity for having frequent measurements made of his machine is stressed in order that he can be sure of its output.

This has been done to a considerable extent in some lesions such as tinea capitis. Other chapters such as the one on angiomas of the skin and epitheliomas need much more elaboration.

The authors have had a tremendous amount of experience and they have done a great deal to elevate the standards of radiation treatment in dermatologic conditions. It is hoped, therefore, that in any subsequent editions more detailed consideration of treatment techniques will be included.

Many of the references in the Bibliography refer to older publications on the various subjects. Though these are important, the Reviewer believes that it is equally important to deal with some of the more recent pathologic considerations of the conditions and the radiologic methods employed in their control.

This is one of the best books on the subject. It contains a wealth of information, is concisely written, and well illustrated. The publishers are to be congratulated on the physical quality of the book including the paper, print and illustrations.

E. P.

MEDICAL CLINICS OF NORTH AMERICA. Boston Number. Philadelphia: W. B. Saunders, 1946. Price, \$16.00 a year.

THIS issue is described as a Symposium on Specific Methods of Treatment. It contains articles on a wide variety of diseases, and will prove of value to the internist as well as to the general practitioner. Some of the papers discuss the present status of new drugs, such as streptomycin, demerol, benadryl and pyribenzamine. Others cover adequately and in sufficient detail such general problems as virus diseases, essential hypertension, renal insufficiency, coronary occlusion, and chemotherapy in diseases of the ear, nose and throat. The paper on infectious hepatitis summarizes the recent advances resulting from the careful study of large numbers of cases in the Armed Forces and in civilian hospitals. "Postwar Tropical Diseases" mentions the problems which will arise from time to time in civilian practice, but fails to give specific directions for the treatment of an average case of malaria, and mentions only in general terms the treatment of amebiasis, which may well prove to be a far more important problem. If the recommendations for the treatment

of anemia and of neurocirculatory asthenia were more widely followed, such patients would be greatly benefited. H. H.

EARLY AMBULATION AND RELATED PROCEDURES IN SURGICAL MANAGEMENT. By DANIEL J. LEITHAUSER, M.D., F.A.C.S., Chief of Surgery, St. Joseph Mercy Hospital, Detroit. Pp. 232; 36 figs.; 6 tables. Springfield, Ill.: Charles C Thomas, 1946. Price, \$4.50.

DURING the recent war the Reviewer had an opportunity to see the effects of an extreme form of early ambulation in many hundreds of Chinese patients who refused to limit their activities after operation. A walk of a mile or so on the day after an abdominal operation was not unheard of. It would be well for a surgeon who has any doubts as to the benefit of early ambulation to read and reread this book until convinced that this method of treatment is not only harmless but beneficial.

There is so much of value in this presentation that it seems petty to call attention to minor inaccuracies and omissions, but there is one suggestion that might be made. If another edition is contemplated, Dr. Leithauser might well expand the section on preoperative management, placing more emphasis on nutrition, for this is of great importance to the patient in the postoperative period. I. R.

MONGOLISM AND CRETINISM. A Study of the Clinical Manifestations and the General Pathology of Pituitary and Thyroid Deficiency. By CLEMENS E. BENDA, M.D., Director, Wallace Research Laboratory for the Study of Mental Deficiency, Wrentham, Mass., Instructor in Neuropathology, Harvard Medical School. Pp. 310, 103 ills. New York: Grune & Stratton, 1946. Price, \$6.50.

THIS book represents data collected during 10 years of research. More than 300 patients with mongolism were studied, 50 of whom came to autopsy. The author gives evidence for his concept of mongolism as pituitary deficiency occurring in fetal life, with growth disturbances following specific patterns, at least, that the mental deficiency is the result of a clinical deficiency of oxytocin or somatomedin.

He states that a degenerating goiter in

cretinism sometimes causes toxic symptoms of "dysthyroidism" and makes total thyroidectomy preferable to leaving intact the degenerating goiter which causes dysfunction. This is not consistent with modern views that thyroid secretion is never an abnormal secretion qualitatively but varies only quantitatively.

Theoretical discussions, such as those dealing with the functional significance of histologic changes in pituitary and thyroid, are not convincing. However, anyone interested in these 2 conditions will find readily accessible the author's extensive data on gross and microscopic alterations in organs, especially those of internal secretion, the brain, and osseous system, roentgen ray findings, metabolic, hematologic and biochemical studies, behavior and maternal condition. These factual data can be separated from personal points of view and interpretations with which some readers will not be in agreement. I. Z.

THE SURGICAL TECHNIC OF ABDOMINAL OPERATIONS. By JULIUS L. SPIVACK, M.D., LL.D., Associate Professor of Surgery, Univ. of Illinois Coll. of Med. 4th ed. Pp. 712; 682 ills. Springfield, Ill.: Charles C Thomas, 1946. Price, \$10.00.

THIS textbook is now in its 4th edition. It is a precisely written and carefully printed book on operative technique. The illustrations are diagrammatic rather than anatomic.

The Reviewer believes that in the next edition the author should feel it his responsibility to eliminate from it futile and even dangerous operative procedures. There is no place in a modern surgical technique book for a description of the use of the Murphy button or for gastroplication. These and a number of other methods belong in a history of surgery.

It might be pointed out also that certain anatomic inaccuracies should be corrected. Figure 235, for example, carries the title "fundus-ectomy;" but the clamps are shown applied to a section of the body of the stomach below the fundus. Again in Figure 303 the greater curvature is shown lying over the pedicle of the spleen with the fundus well out of the operative field; but the text, referring to the illustration, cautions against injury to the fundus.

In spite of these criticisms the book has the virtue of clarity and conciseness and is undoubtedly useful to interns and residents as a visual aid to understanding the procedures to be followed in the operations described.

I. R.

THE DIAGNOSIS AND TREATMENT OF BRONCHIAL ASTHMA. By LESLIE N. GAY, PH.B., M.D., Assistant Professor of Medicine of the Johns Hopkins University, School of Medicine, Director of the Allergy Clinic of the Johns Hopkins Hospital. Foreword by WARFIELD T. LONGCOPE, A.B., M.D., Professor of Medicine of the Johns Hopkins University School of Medicine, Physician-in-Chief of the Johns Hopkins Hospital. Pp. 334; 80 ills.; 4 plates. Baltimore: Williams & Wilkins, 1946. Price, \$5.00.

A SOUND presentation of a complex subject and in keeping with the training and rich experience of the author. Chapters deal with the physiology of normal respiration and the asthmatic state, the etiology of asthma, its pathology, its diagnosis, the complications and differential diagnosis of asthma, asthmatic paroxysms, due to psychosomatic disturbances, and the treatment of asthma. Particularly well done are the chapters on pathology and on treatment. There are numerous illustrative case reports that enhance the value of the book. The many therapeutic measures that have been used in this disease are evaluated and the advice offered is conservative and dependable. The discussion of the relation of psychosomatic disturbances to asthma is perhaps more favorable to the psychiatric approach than the evidence warrants, but is fairly put. General practitioners and allergists will find it a helpful addition to their library.

R. K.

ACTIONS AND USES OF DRUGS, A TEXTBOOK FOR NURSES. By WINDSOR C. CUTTING, M.D., Professor of Therapeutics, Stanford University. Pp. 326; 27 ills. San Francisco: Stanford Univ. Press, 1946. Price, \$3.00.

CONSIDERING the limitations of background of student nurses and the time usually allotted to a nurse's course in Pharmacology, this text seems to be a most sensible approach to the subject. The fact that the book does not adhere closely to the course

outline given in *A Curriculum Guide for Schools of Nursing* and the omission of many rather obsolete drugs, often included in this course, are well compensated for by the logical, basic approach to this science and by the inclusion of many of the newer drugs in wide use today. Each illustration is simple, meaningful and enlightening.

H. R.

NEW BOOKS

Chemotherapeutic and Other Studies of Typhus. By M. VAN DEN ENDE, C. H. STUART-HARRIS, F. FULTON and J. S. F. NIVEN, *et al.* Medical Research Council, Special Report Series No. 255. Pp. 246; 11 ills. London: His Majesty's Stationery Office, 1946. Price, \$3.65.

A Laboratory Manual of Physiological Chemistry. By WILSON D. WRIGHT. 6th ed. Pp. 275. Baltimore: Williams & Wilkins, 1947. Price, \$2.50.

The Story of Human Birth. By ALAN FRANK GUTTMACHER, M.D. Pp. 224; 7 ills. New York: Penguin Books, 1947. Price, \$0.25.

A REPRINT of Dr. Guttmacher's book entitled "Into This Universe."

Neue Wege in der Diagnostik und Therapie der Lues. By A. ROTTMAN. Pp. 128. Vienna: Verlag Brüder Hollinek, 1946. Price, \$9.50.

Chemotherapeutic and Other Studies of Typhus. Special Report Series No. 255. Price, \$3.65.

Primeros Cuidados a un Accidentado. Por El Dr. L. GUBERN SALISACHS, Exprofessor A. por oposicion de la Facultad de Medicina de Barcelona. *Complicaciones de la obesidad.* Por el Dr. RICHARD A. FAUST. *Diagnostico precoz del carcinoma uterino.* Por el Dr. JOE VINCENT MEIGS. *Indicaciones y forma de aplicación de penicilina en dermatología.* Por el Dr. M. CASANOVAS. Pp. 203; 65 ills. Barcelona: Coleccion Espanola de Monografias Médicas. Vol. 58, 1946. No price given.

Compresiones Medulares. Coleccion Espanola de Monografias Médicas. Vol. 55. Por el Dr. IGNACIO DE GISPERT CRUZ. Pp. 135; 39 ills. Barcelona: Ediciones Byp, 1946. Price not given.

Tratamiento Actual de la Sífilis. Coleccion Espanola de Monografias Médicas. Vols. 56-57. Por el Dr. MODESTO CASANOVAS. Pp. 169. Barcelona: Ediciones Byp, 1946. Price not given.

Étude des troubles causés par la dénutrition dans un asile d'aliénés. Par MARCEL BACHET, Externe en premier des Hôpitaux de Paris, Interne de la Maison de Charenton. Pp. 269. Paris, Louis Arnette, 1943. No price given.

Three books by D. DANIELOPOLU, Professeur de Clinique Médicale à la Faculté de Médecine de Bucarest:

Le Système Nerveux de la Vie Végétative. I-ère Monographie. *Schema Anatomophysiologique du Système Nerveux de la Vie Végétative.* Pp. 443; 159 ill., 1944.

Phylaxie Paraphylaxie et Maladies spécifiques. Pp. 285; 91 ill., (n.d.).

La Digitale et les Strophantines. Pp. 206; 56 ill., 1946.

Paris: Masson et cie. No prices given.

Chemotherapy, Yesterday, Today and Tomorrow. The Linnere Lecture 1946. By SIR ALEXANDER FLEMING. Pp. 39; 2 ill., 5 figs. Cambridge: University Press; New York: Macmillan, 1946. Price, \$5.50.

Directory of Medical Specialists Holdings Certification by American Boards. Vol. III. Edited by PAUL TITUS, M.D., and associates. Pp. 896. Chicago: A. N. Marquis, 1946. No price given.

Besides including all the changes to date of the examination requirements of all Boards, this 3rd edition contains "much entirely new biographic information."

Tumores y Scudotumores de la Mama. Por el Dr. JACINTO MORENO. Pp. 139; 40 ill. Buenos Aires: Lopez & Etchegoyen S.R.L., 1947. No price given.

A BRIEF review of the pathology, a discussion of the classification and a rather pessimistic view of the therapeutic possibilities based on personal impressions.

La Enfermedad de Boeck. Boeck Schapmann. By ST. J. LEITNER. Colección Española de Monografías Médicas, Vols. 59-60. Pp. 240; 37 ill. Barcelona: Ediciones Byp, 1946. No price given.

A SWEDISH translation of the German language monograph published in Bern, Switzerland, in 1942. It is based on a study of 15 cases and an exhaustive review of the literature, especially European. The clinical and classificatory aspects are particularly well covered. The question of tuberculous or non-tuberculous etiology is unhesitatingly considered and left undecided. This small volume presents a thorough coverage of the subject. The illustrations leave much to be desired technically.

NEW EDITIONS

Handbook of Microscopic Characteristics of Tissues and Organs. By KARL A. STILES, M.S., Ph.D., Professor of Biological Science, Michigan State College. With an Introduction by MELVIN H. KNISLEY. 3rd ed. Pp. 214; 33 ill. Philadelphia: Blakiston, 1946. Price, \$1.75.

This handbook attempts to separate the subject matter required for immediate use from that needed for reference. It "is designed to be used supplementary to a regular textbook of histology. . . . It may be used as a syllabus with lectures. It can be used as a laboratory manual. . . . It has proved its worth for purposes of review to students of pathology."

Principles of Animal Biology. By A. FRANKLIN SULL, Professor of Zoology, University of Michigan, in collaboration with GEORGE R. LARUE and ALEXANDER G. RUTHVEN. 6th ed. Pp. 425; 305 ill. New York: McGraw Hill, 1946. Price, \$4.00.

This edition of a useful book includes changes that stress the modern preoccupation with function.

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

JUNE, 1947

ORIGINAL ARTICLES

POST-EXERTIONAL ORTHOSTATIC HYPOTENSION

By LUDWIG W. EICHNA, M.D.*

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AND

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TRANSITORY non-fatal collapse following severe physical effort is a familiar phenomenon in competitive sport. Jokl⁷ has described the clinical picture of this "Sportkrankheit" and Mateef and Petroff⁸ and Mateef⁹ first described and studied the orthostatic hypotension which is one of its circulatory aspects. Brogdon and Hellebrandt,² Eichna and Bean,³ Mayer-son,¹⁰ Allen, Taylor and Hall¹ have confirmed the occurrence of orthostatic hypotension following hard muscular work. However, observations dealing with the nature of this postural hypotension are still few. While studying the physiologic effects induced in healthy young men worked to the limits of their physical tolerance, we encountered post-exertional orthostatic hypotension and had an opportunity to study it. Some of these studies are here presented.

Subjects and Methods. The subjects were all young, healthy soldiers (enlisted men) undergoing some phase of military training beyond basic training. They were, therefore, physically more fit than the usual normal group drawn from civilian life. The required work was performed at all hours

of the day, except immediately after meals, and consisted of exercise tests designed to determine physical fitness. Two of the tests, the pack test and the treadmill test, were of the acute, exhausting type; the third, the hike, was of the long, enduring type. In the pack test,⁵ the subjects stripped to shorts, socks and shoes, and carrying a pack weighing one-third of their body weight, stepped up and down on a platform 16 inches high, once every 2 seconds for 5 minutes, unless exhaustion forced them to discontinue before that time. In the treadmill test,⁶ the subjects, similarly clothed but without pack, ran on a motor-driven treadmill for 5 minutes, unless forced by exhaustion to discontinue before that time. The speed of the treadmill was 7.5 miles per hour for the initial tests and 5.6 miles per hour for the repeat tests; in all tests the treadmill grade was 8.6%. The physical effort of these 2 tests is such that approximately one-third to one-half of the healthy young men attempting them fail to complete the required 5 minutes of work. In the hike, the men wore regulation fatigue uniforms of herringbone twill, carried packs weighing 20 pounds and were required to walk 32 miles in the best time they could, usually 7 to 9 hours. The pack and treadmill tests were performed indoors at an ambient temperature of about

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74° F. The hike tests were performed on the open road in the moderately warm weather of late spring. On completing the pack and treadmill tests, the men sat down for 5 minutes before postural studies were begun. In the hike tests these studies were started immediately after finishing the march.

Except after several of the hikes, when men changed from the lying to erect (90 degree) position by their own effort, position was always changed passively by means of a tilt table. The erect position was 70 degrees erect with the weight supported by the legs. No attempt was made to diminish postural sway or movement, other than repeated admonitions to stand still. Position was changed alternately from erect (70 degrees) to flat and flat to erect (70 degrees) at 5 minute intervals, except when syncope shortened the time in the erect position. While in each position the heart rate (by palpation or auscultation) and blood pressure (by auscultation, using a mercury manometer) were simultaneously and repeatedly determined, usually at 30 to 60 second intervals. At least one set of determinations in the flat and erect (70 degree) positions preceded an exercise test. Following exercise, all subjects were observed through at least 2 erect periods, separated by 1 in the supine, and thereafter through as many changes of position as the individual case required. In certain instances respiratory rates, vital capacities, and electrocardiograms were taken in each position before and after exercise.

In a number of subjects the relationship between their postural responses after exercise and their cardiovascular lability was studied by determining the changes in heart rate and blood pressure induced by several stimuli administered in the control period: (a) posture test, change from supine to erect (70 degrees); (b) cold pressor test, immersing one forearm in ice water for 2 minutes; (c) mental pressor test, requiring the subject to do arithmetical problems (multiply 3 digits by 2 digits) in his head for 5 minutes; (d) exercise test, changes during the 5 minutes immediately on completion of standard exercise.

Results. The post-exertional orthostatic responses are divided into 3 groups: syncope, abnormal and normal. The *syncope*

group includes those subjects who developed syncope and were unable to remain erect for 5 minutes during either one or both of the 2 required erect periods after exercise. While erect, their blood pressures were usually very low and their heart rates rapid but collapse rather than any level of blood pressure or heart rate was the criterion for inclusion in this category. When upright, these subjects developed the typical symptoms and signs of syncope, either singly or in varying combinations, and in varying intensity. Almost invariably present were marked fatigue, drowsiness, apprehensiveness, increasing discomfort, nausea, abdominal cramps, lightheadedness and dizziness, and the sensation of impending collapse. In the more severe instances, dimness of vision progressing to tubular vision and "blackout," vomiting, disorientation, inability to move or obey commands even though hearing them progressed to complete loss of consciousness and crumpling at the knees, at which time the men were tilted flat. These symptoms were accompanied by various signs, yawning, deep breathing, increasing pallor leading to a pallid ashen cyanosis, profuse sweating, gasping respiration, apprehensive restlessness or listlessness, a steadily falling blood pressure with very narrow pulse pressure, markedly decreased intensity of heart sounds, and a rapid, weak pulse. Just before consciousness was lost, and the subject tilted supine, the heart in a number of subjects slowed markedly. Once supine, all symptoms quickly improved or disappeared completely. For a short time immediately after becoming supine, a marked bradycardia and elevation of blood pressure were often encountered, but as the supine position was maintained both heart rate and blood pressure returned to normal.

The *abnormal* group includes those subjects who were able to remain erect for the required 5 minutes during both of the post-exertional erect periods, but who, during at least 1 of them, sustained a fall in systolic blood pressure to abnormally

low levels, here defined as 100 mm. Hg or less, provided that that level was at least 10 mm. Hg lower than the lowest pre-exercise, erect, systolic blood pressure. Many men developed symptoms and signs similar to those in the syncopal group. Usually they were more mild but in some instances they were so severe that the men were just able to remain erect for the required 5 minutes. If the erect period had been further prolonged some men would surely have fainted. Others had no symptoms though severely hypotensive.

The *normal* group includes all of the others, men who remained erect after exercise without symptoms and with systolic blood pressures above 100 mm. Hg.

group, and for the same group order an increasing, but less striking, rise in heart rate. Syncope was most closely related to the systolic blood pressure and was most likely to occur when it fell to about 80 mm. Hg. Pulse pressure bore less relationship to syncope: the pulse pressure for the abnormal group was as low, and even lower, than that for the syncopal group (second erect period, Table 1). Circulatory failure in the erect position was more marked, as a rule, in the second erect period, 15 to 20 minutes after the cessation of exercise, than in the first erect period, 5 to 10 minutes after work. This is indicated by the greater number of syncopes and the greater fall in blood pressure

TABLE 1.—BLOOD PRESSURE, HEART RATE AND DURATION OF ERECT POSTURE AFTER ACUTE EXHAUSTING WORK

(The data for each group are averages of the final readings taken before position of subject was changed)

Group	No. subjects	First erect period					Supine period (5 min.)				Second erect period				
		Duration (min.)	Blood pressure (mm. Hg)			Heart rate (per min.)	Blood pressure (mm. Hg)				Duration (min.)	Blood pressure (mm. Hg)			Heart rate (per min.)
			Syst.	Diast.	Pulse		Syst.	Diast.	Pulse	Heart rate (per min.)		Syst.	Diast.	Pulse	
Normal	14	5 0	119	88	31	115	117	73	44	100	5.0	114	90	24	112
Abnormal	10	5 0	103	76	27	116	117	67	50	105	5.0	95	83	12	116
Syncopal	0	2 4	*98	*72	*26	*122	118	68	50	108	2.6	†81	†64	†17	118

* Average of the 4 subjects with obtainable blood pressure; blood pressure unobtainable in 5 subjects.

† Average of the 5 subjects with obtainable blood pressure; blood pressure unobtainable in 4 subjects.

‡ Average of the 6 subjects with obtainable blood pressure; blood pressure unobtainable in 3 subjects.

° Average of 8 subjects; pulse missing on 1 subject.

ORTHOSTATIC HYPOTENSION FOLLOWING ACUTE EXHAUSTING PHYSICAL WORK. Since the pack test and treadmill test both required essentially the same type of physical effort and produced very similar findings, the results of these 2 tests are combined into one analysis.

Type of Response and Incidence. Of 33 men subjected to acute exhausting physical work approximately one-half (19 or 57.6%) developed post-exertional orthostatic hypotension, with 9 (27.3%) in the syncopal group and 10 (30.3%) in the abnormal group (Table 1). Thus, every other man developed post-exertional orthostatic hypotension and 1 man in 4 had syncope. Table 1 indicates the progressive fall in blood pressure from the normal through the abnormal to the syncopal

in the second erect period than in the first (Table 1). The similarity in blood pressures for all 3 groups when the subjects were supine indicates that the circulatory disturbance is apparent only in the erect position.

Chart 1 indicates the response of a man in the normal group. Charts 2 and 3 are typical of 2 types of syncopal responses. In Chart 2 the hypotension and syncope develop "immediately," in the first erect period, but nevertheless, become more severe in subsequent upright periods. In Chart 3 the onset of hypotension and syncope are "delayed." The first erect period is tolerated without difficulty and with sustained blood pressures and heart rates. Hypotension and syncope develop in this second erect period and remain

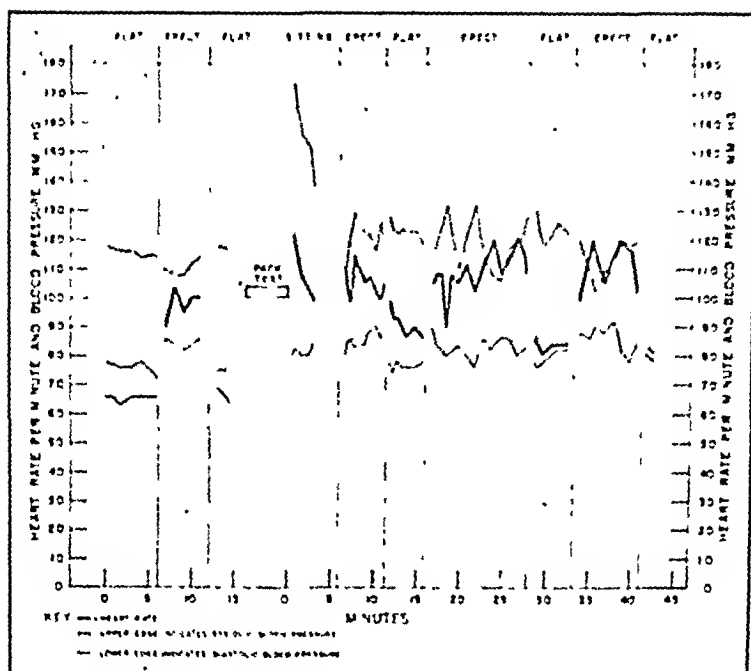


CHART 1.—Normal blood pressure in the erect posture following acute exhausting exercise. In this and subsequent charts the heavy black line indicates the heart rate; the upper level of the shaded area the systolic blood pressure; the lower level of the shaded area the diastolic blood pressure.

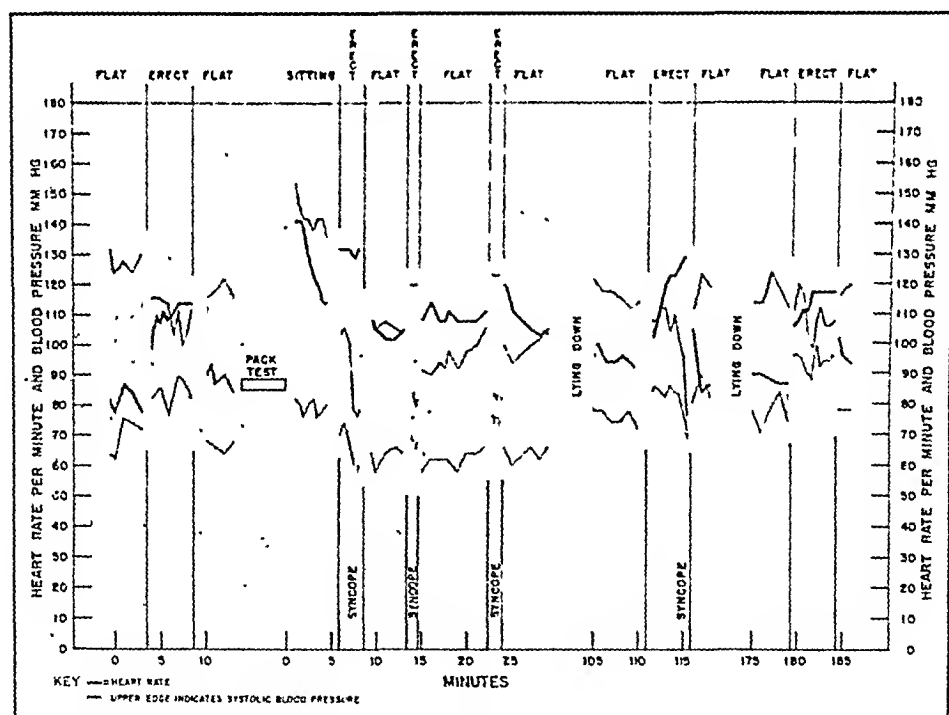


CHART 2.—Orthostatic hypotension with syncope following acute exhausting exercise. The hypotension and syncope develop during the first erect period after exercise and are still present 2 hours after cessation of effort.

severe thereafter. Usually tachycardia accompanies the hypotension (Chart 2) but at times the heart slows just as collapse is about to occur (Chart 3). In 1 instance (Chart 3 at point X) such a cardiac slowing progressed to an asystole of 19 seconds, with collapse of the subject.⁴

In another subject (Chart 2) orthostatic syncope still occurred almost 2 hours after the exercise. Three hours after work, the erect posture was tolerated for 5 minutes, but the blood pressure was not yet normal. As a rule, there was recovery from syncope within 1 hour and from

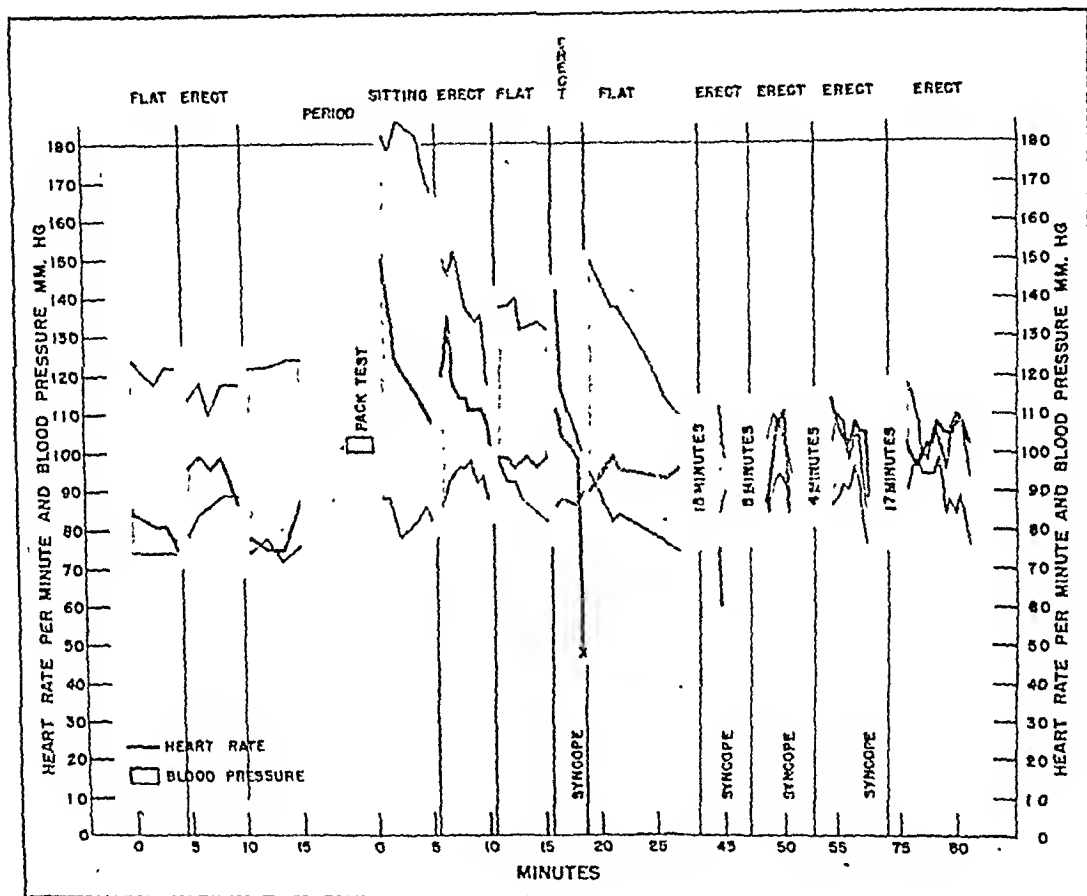


CHART 3.—Orthostatic hypotension with syncope following acute exhausting exercise. The hypotension and syncope are delayed in appearance and do not develop until the second erect period, following a first erect period which was tolerated without difficulty. Terminal bradycardia accompanied the hypotensive episodes.

Duration. The duration of the post-exertional orthostatic hypotension varies but it tends to persist for an unexpectedly long time. Thus in 1 subject (Chart 3) orthostatic hypotension with syncope was still present 1 hour after stopping work and it was not until 1 hour and 15 minutes after the exertion that he could remain erect for the required 5 minutes. Even then the blood pressure had not yet returned to normal but fluctuated widely, with low systolic and narrow pulse pres-

sure. In another subject (Chart 2) orthostatic syncope still occurred almost 2 hours after the exercise. Three hours after work, the erect posture was tolerated for 5 minutes, but the blood pressure was not yet normal. As a rule, there was recovery from syncope within 1 hour and from

Type of Subject. The physical characteristics of the subjects and their cardiovascular responses to various stimuli gave little basis for predicting who would develop this syndrome. There were but

minimal differences in the physical characteristics of the subjects of the 3 groups (Table 2). The men in the syncopal group averaged slightly taller (3 inches) and heavier (12 pounds) than the men in the normal group. There were no significant differences in the ages of the 3 groups. Physical fitness, as determined by fitness tests, was essentially the same in all 3 groups (Table 2). There were only slight differences in the cardiovascular responses to stimuli. Perhaps the responses in the syncopal group may be considered somewhat more labile than those in the other 2 groups (Table 3). The most marked

Thus, of 5 subjects who were in the syncopal group after the first test, only 1 remained in the syncopal group following a repeat test; 2 moved into the abnormal group and 2 into the normal group. Similarly, of 7 subjects in the abnormal group after the first test, only 3 remained in the abnormal group following a repeat test, while 4 moved into the normal group. Ten men in the normal group on the first test remained in the normal group on repeat tests. In all instances the physical fitness scores were not significantly different on repeat tests from those on the initial tests.

TABLE 2.—PHYSICAL CHARACTERISTICS AND PHYSICAL FITNESS OF THE SUBJECTS
(Data are the average for each group)

Group	No. subjects	Physical characteristics			Physical fitness	
		Age (yrs.)	Height (ft., in.)	Weight (lbs.)	Time of effort (min.)	Fitness score
Normal	14	26	5'6"	152	3.5	59
Abnormal	10	22	5'6"	155	3.4	52
Syncopal	9	23	5'9"	164	3.8	52

TABLE 3.—COMPARISON OF THE CARDIOVASCULAR RESPONSES OF THE THREE GROUPS TO STIMULI
(The data for each group are averages of the most marked response during the stimulus)

Group	No. subjects	Supine				Erect (70°)				Cold pressor test*				Mental problem†				Exercise‡			
		Blood pressure (mm. Hg)		Heart rate (per min.)		Blood pressure (mm. Hg)		Heart rate (per min.)		Blood pressure (mm. Hg)		Heart rate (per min.)		Blood pressure (mm. Hg)		Heart rate (per min.)		Blood pressure (mm. Hg)		Heart rate (per min.)	
		Syst.	Diast.	Pulse		Syst.	Diast.	Pulse		Syst.	Diast.	Pulse		Syst.	Diast.	Pulse		Syst.	Diast.	Pulse	
Normal	14	110	73	46	71	118	85	33	91	131	91	43	71	135	92	43	89	166	78	88	145
Abnormal	10	117	73	44	71	112	83	29	94	134	92	42	74	129	86	43	86	149	69	80	166
Syncopal	9	122	73	49	77	115	86	29	101	141	98	43	70	136	88	48	67	158	75	83	172

* Two minutes of immersion of forearm in iced water.

† Five minutes of mentally multiplying 3 digits by 2 digits.

‡ Immediately on termination of pack test, subject seated.

differences lay in the higher pulse rates immediately after acute exhausting work and in the greater pressor response to the cold test in the syncopal group.

The data suggest that post-exertional hypotension is more likely to occur in the tall, heavy subject with labile cardiovascular responses. The small number of subjects requires that this suggestion be taken with reservation.

Repeat Tests. With repetition of the work on subsequent days there is a tendency for improvement, and even disappearance, of the post-exertional orthostatic hypotension and syncope (Chart 4).

Mechanism of the Hypotension. Several simple observations indicated the major rôle played by the motionless, dependent lower extremities in the production of the hypotension.

With the trunk still erect, raising the lower extremities to a horizontal position, so that the heels were on the same level as the buttocks materially raised the blood pressure (Chart 5). This maneuver did not, however, return the blood pressure to normal. A definite hypotension (abnormal group) still persisted but it was not so severe as to cause syncope. Syncope, however, promptly recurred when the legs

were lowered to the dependent position (Chart 5). Apparently the distribution of blood in both the splanchnic area and in the legs is responsible for the orthostatic hypotension and dependency of the lower extremities is critical to the production of the full effect.

static hypotension promptly returned (Chart 6).

When blood is prevented from flowing into the lower extremities of the upright subject, orthostatic hypotension does not occur; the blood pressure is sustained and a previously syncopal subject remains

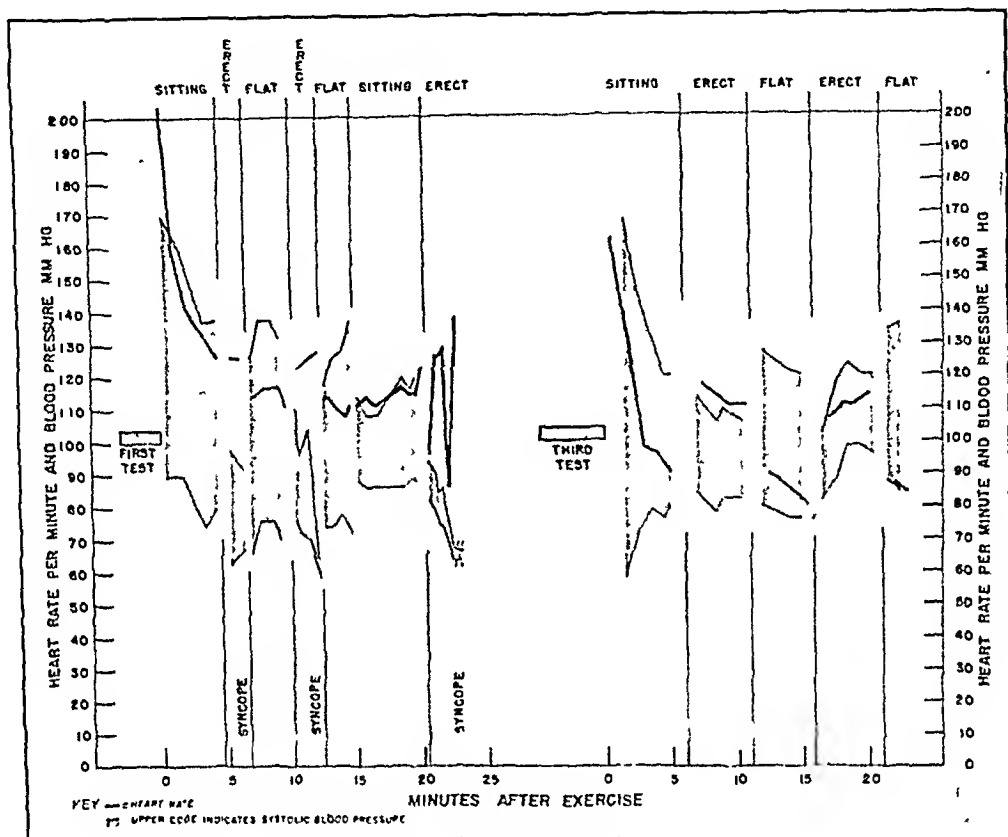


CHART 4.—Disappearance of post-exertional orthostatic hypotension with repetition of the inducing acute exhausting exercise. Marked orthostatic hypotension after the first test; normal blood pressure when erect after the third test.

During the orthostatic hypotension, movement of the fully dependent legs, without the accomplishment of much additional work, caused the blood pressure to rise from its low level to higher, and even normal, levels which were maintained as long as movement of the legs was continued (Chart 6). The movement of the legs here used consisted of bending the knee forward sufficiently for the heel to clear the foot board of the tilt table, the toe retaining contact with it. The legs were moved one at a time and alternately. With cessation of their movement ortho-

erect without difficulty (Chart 7). Just before the subject was tilted erect, the circulation to both legs was occluded by suddenly inflating, without venous stasis, blood pressure cuffs encircling both thighs. The cuffs were of standard 13 cm. width, backed by heavy cloth so that they did not balloon, and were inflated to 240 mm. Hg from pressure bottles. With the cuffs thus inflated orthostatic hypotension did not occur but it developed rapidly in preceding and subsequent erect periods when the thigh cuffs were not inflated (Chart 7).

Trapping as much blood as possible in

both lower extremities of a non-exercised subject failed to produce definite orthostatic hypotension, although some lowering of the systolic pressure and narrowing of the pulse pressure did occur (Chart 8). Reactive hyperemia was utilized to produce full dilatation of the vascular beds of the legs in which the blood was then

cuffs were deflated to zero, permitting accumulation of blood in the dilated vascular beds of the legs under the influence of gravity alone; in the second instance they were deflated to 50 mm. Hg, trapping the blood under the influence of this resisting barrier as well as gravity. Chart 8 shows the marked

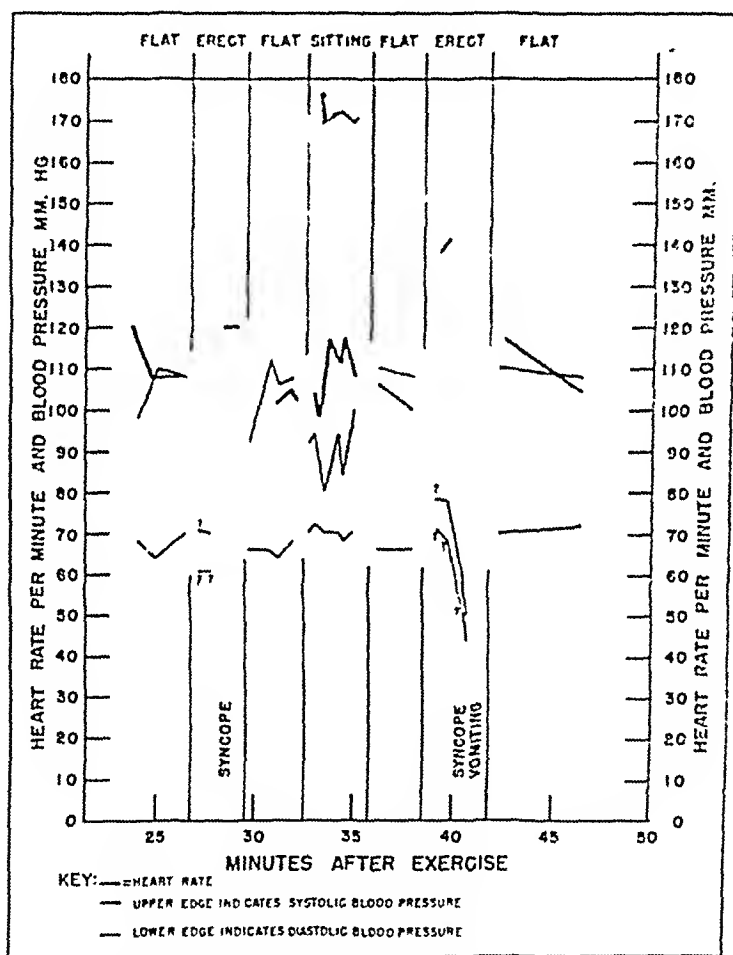


CHART 5.—Improvement in the post-exertional orthostatic hypotension when the legs are raised to a horizontal position at the level of the pelvis. (Indicated by diagram at top of sitting column.)

trapped. With the subject flat, blood pressure cuffs about both upper thighs were inflated to 240 mm. Hg occluding the circulation to both legs. After 10 minutes the subject was tilted erect and 1 minute later both cuffs were deflated producing marked hyperemia of the dependent legs. In the first instance the

drop in blood pressure immediately at the onset of reactive hyperemia and then the spontaneous and rapid recovery to a higher level, presumably as a result of vasoconstriction of other vascular areas of the body. The subject then remained erect without symptoms, in spite of the pooling in the legs of presumably as much

blood as their vascular beds would hold. This subject developed orthostatic hypotension following the pack test.

ORTHOSTATIC HYPOTENSION FOLLOWING PROLONGED ENDURING PHYSICAL EFFORT. Limited observations made after the completion of long-sustained physical work of lower energy expenditure indicated that

tional orthostatic hypotension; 5 men (20.8%) were in the syncopal group and 8 men (33.3%) in the abnormal group (Table 4, Chart 9). This incidence is similar to that after acute exhausting exertion. After the hike test, the second erect period was omitted except in those subjects who developed hypotension dur-

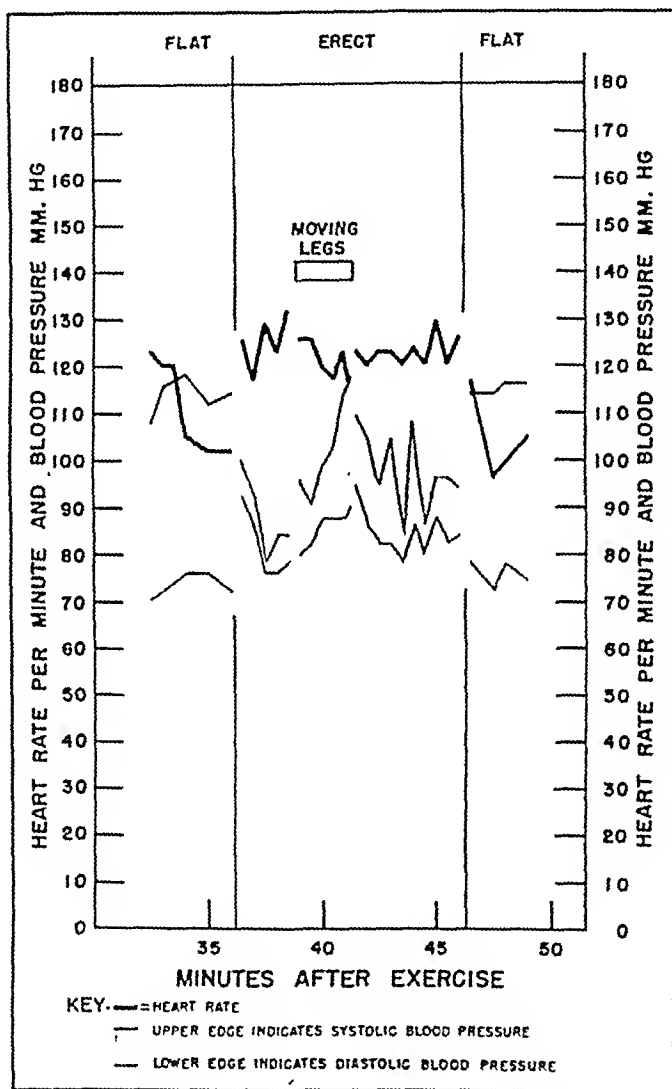


CHART 6. —Improvement in the post-exertional orthostatic hypotension when the dependent legs are moving.

post-exertional orthostatic hypotension occurs after this type of work as well as after acute exhausting physical effort. The 32 mile hike was attempted by 24 men; 22 finished, 2 dropped out after 28 miles. The responses of these 2 men are grouped with the others. Of the 24 men, 13 (54.2%) developed post-exer-

ting the first erect period and it is possible that late developing hypotensions were missed.

The orthostatic hypotension induced by prolonged enduring work was very similar to that after acute exhausting work. Its development bore no relationship to the height, weight or age of the subjects

(Table 4) or to their physical fitness as determined by fitness tests and their general work performance. As after acute exhausting work, the orthostatic hypotension following the endurance hike often persisted for a long time. Usually the ability to remain erect, with a sustained

blood pressure and without symptoms, returned in 1 to 2 hours after stopping work (Chart 9). In 1 instance, orthostatic hypotension was still present after a night's sleep, 12 hours after finishing the hike, and it was not until 16 hours after the hike that the erect posture could be main-

TABLE 4.—PHYSICAL CHARACTERISTICS OF THE SUBJECT GROUPS AND THEIR CARDIOVASCULAR RESPONSES AFTER 32 MILE HIKE

(The data for each group are averages of the final readings taken before position of subject was changed)

Group	No subjects	Physical characteristics			First erect period				Second erect period					
					Blood pressure (mm Hg)			Heart rate (per min)	Blood pressure (mm Hg)			Heart rate (per min)		
		Age (yrs.)	Height (ft., in.)	Weight (lbs.)	Duration (min.)	Syst.	Diast.		Pulse	Duration (min.)	Syst.		Diast.	Pulse
Normal	11	23	5'8"	152	3.0	114	85	29	110					
Abnormal	8	22	5'8"	155	5.0	94	70	15	114					
Syncopal	5	25	5'7"	157	2.7	*92	*82	*10	120	2.0	†70	†68	†11	105

* Data for the 1 subject with obtainable blood pressure; blood pressure unobtainable in 4 subjects.

† Average of the 3 subjects with obtainable blood pressure; blood pressure unobtainable in 1 subject, and second erect period omitted on 1 subject.

‡ Average of 4 subjects; pulse missing on 1 subject.

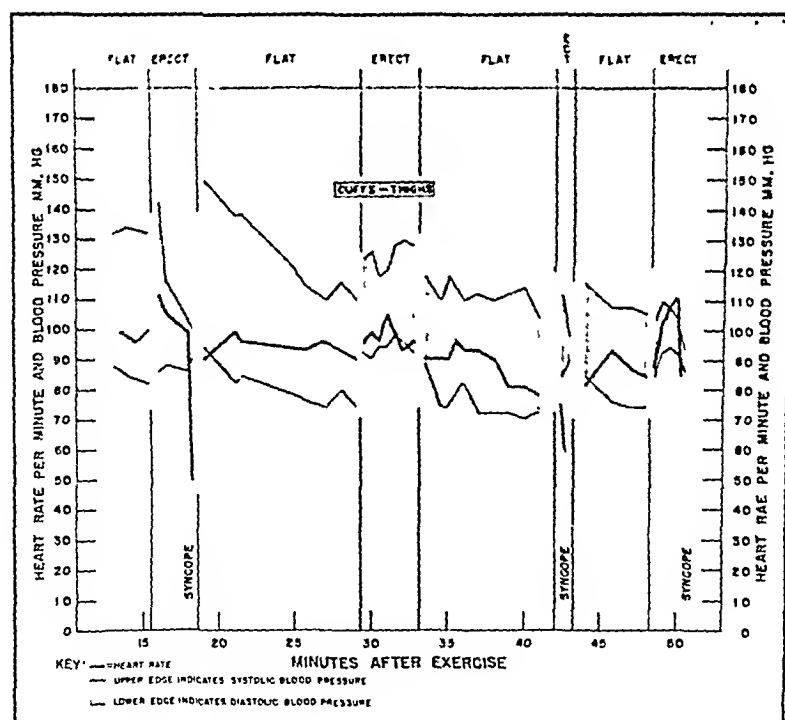


CHART 7.—Prevention of post-exertional orthostatic hypotension by excluding the circulation to the dependent legs. Just before the subject is tilted erect the cuffs about the thighs are inflated to 240 mm. Hg.

tained for 5 minutes. Even then the blood pressure was abnormal (Table 5). This subject also developed orthostatic hypotension after the pack test.

tered orthostatic syncope in 17 (17%) of 100 aviation cadets who had run to exhaustion on a treadmill. In all of these studies, including the present one, the

TABLE 5.—PERSISTENCE OF POST-EXERTIONAL ORTHOSTATIC HYPOTENSION IN A SUBJECT FOLLOWING AN ENDURANCE HIKE (32 MILES)

Time	Blood pressure subject erect (70°) (mm. Hg)	Heart rate (per min.)	Duration of erect posture	Remarks
Before hike	114/92	117	5 min.	No symptoms
1 hour after hike	Unobtainable	138	2 min.	Syncope
12 hours after hike (next morning)	Unobtainable	138	3 min.	Syncope
16 hours after hike	100/92	120	5 min.	Feels all right

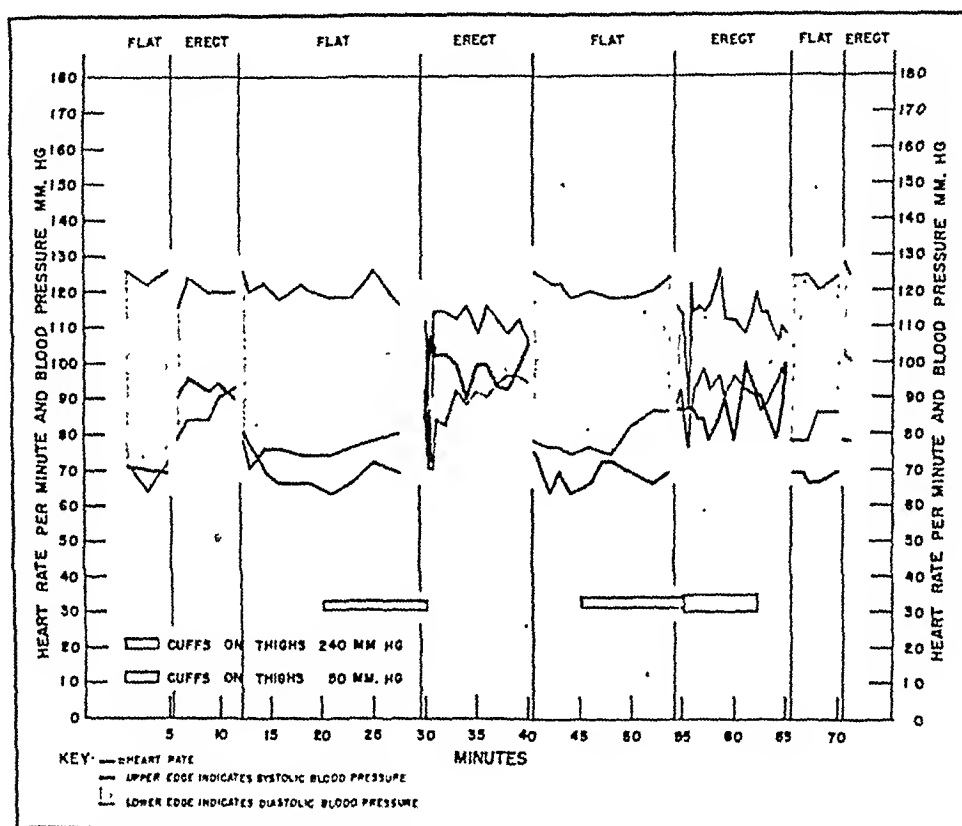


CHART 8.—Failure to produce orthostatic hypotension by trapping maximum amounts of blood in the dependent legs. Reactive hyperemia was used to induce maximal dilatation of the vascular beds of the legs and gravity plus venous occlusion to trap the blood in the dilated vessels.

Discussion. Combining the data following acute exhausting and prolonged enduring work into a group of 57 tests, post-exertional hypotension with syncope occurred in 14 (25%) and hypotension without syncope in 18 (32%). This agrees with the findings of other investigators. In a group of 50 students Mayerson¹⁰ reported post-exertional orthostatic syncope in 17 (34%) and "poor response" in 10 (20%). Allen, Taylor and Hall¹ encoun-

subjects have been healthy, young adult males, at times in especially good physical condition (athletes). One can only guess that the incidence in older age groups might be considerably higher, and the inducing physical effort less severe.

The erect position used in this study tends to minimize the incidence of orthostatic circulatory insufficiency: (a) the erect periods were maintained for only 5 minutes; others have required 10 to

20 minutes, and (b) the body weight was borne by the legs, permitting muscle tonus to aid in the venous return from the legs; others have eliminated this by supporting the body from the pelvis or shoulders. Since the erect man normally supports his weight on his feet, it was felt that observations performed in this manner would come nearer to reproducing the conditions under which this syndrome might occur in everyday life.

explanation an inadequate return of blood to the heart. The beneficial effects resulting from elevating the legs while the trunk remains erect, moving the legs when they are dependent, and excluding the circulation from the dependent legs, all suggest that the circulation in the lower extremities is at fault and responsible for the decreased venous return. The question is the nature of this circulatory fault.

Two possibilities present themselves:

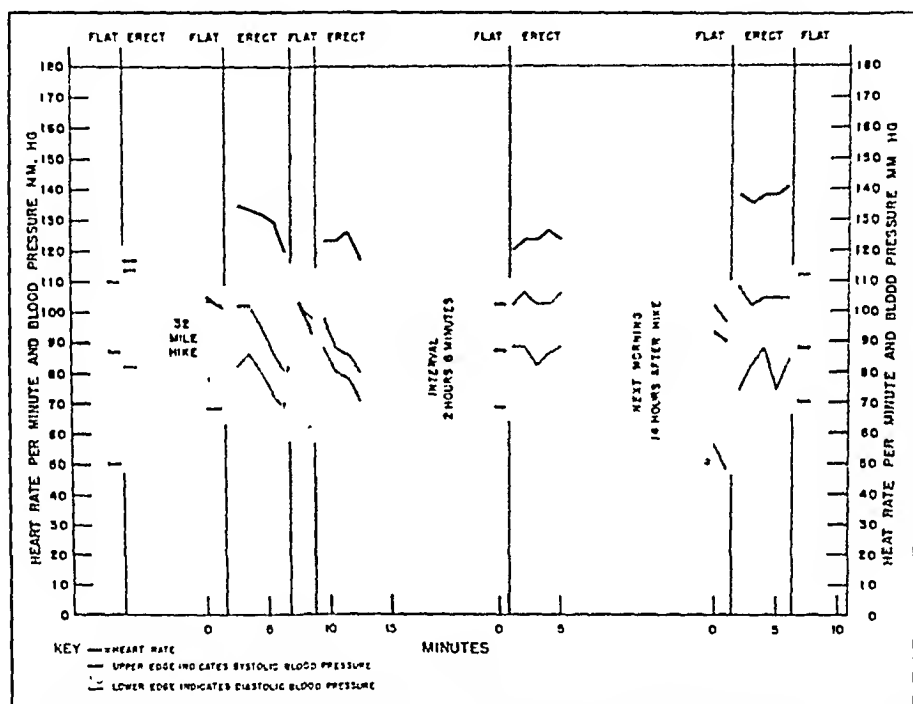


CHART 9.—Orthostatic hypotension with syncope following moderate work of long duration (32 mile hike).

The failure to establish a clear-cut relationship between post-exertional orthostatic hypotension and bodily configuration, tests of cardiovascular lability, or physical fitness gives, at present, no basis for predicting who will develop hypotension after physical effort. It can, however, be prevented by training, through repetition of the inducing physical work.

The present study does not explain completely the mechanism which permits the development of orthostatic hypotension after exertion, but suggests as a plausible

(a) marked vasodilatation of the vascular tree of the legs and (b) failure of the muscular venopressor mechanism in the legs. The first of these assumes such a marked dilatation (exercise induced) of the vascular tree of the legs that the total vascular bed of the body is now disproportionately greater than the blood volume available to fill it at a normal pressure. The vascular tree of legs would contain an excessive amount of blood which would be flowing. The second possibility assumes that such a vasodilatation is not by itself capable

of producing the hypotension, as long as blood flow through the legs persists, and suggests that the blood in the legs has become stagnant through the failure of the muscular venopressor mechanism to move it onward and upward. The blood in the legs would be relatively non-moving. Since both mechanisms would reduce the amount of blood at heart level and induce hypotension, it may be considered an academic point to choose between them. Nevertheless, several observations suggest that failure of the venopressor mechanism may be a more critical factor than extensive vasodilatation. These are: (a) the delayed development of orthostatic hypotension in some subjects who stand without difficulty in the first erect period, when vasodilatation is greatest, and then develop hypotension in subsequent stands when vasodilatation is presumably diminishing (Chart 3); (b) the persistence of the orthostatic hypotension for long periods (several hours) after cessation of exertion, when the vascular dilatation may be considered to have largely passed off (Charts 2 and 3); (c) the recovery of the blood pressure from hypotensive toward normal levels when the dependent legs are moved without significant additional work (Chart 6); and (d) the failure to induce a similar hypotension and syncope when maximum amounts of blood are trapped in the dependent legs of erect but non-exercised subjects, who develop orthostatic hypotension after exercise (Chart 8). In this last instance, the large blood mass in the legs is presumably still moved forward by the unaltered muscular venopressor mechanism of non-exercised legs. While the above observations suggest that a reduced muscular tone with a depressed venopressor mechanism in the legs plays the major rôle in the hypotension, this point has not been substantiated by direct experimentation. Neither has the degree of vasodilatation in the legs been measured.

This study, and similar ones in the literature, have all dealt with work performed either largely or wholly by the lower extremities. The critical, parallel

observations following work of the upper extremities alone have yet to be carried out.

It is desirable to point out again that post-exertional orthostatic hypotension is not limited to acute exhausting effort and that it occurs with almost equal frequency, and with similar physiologic changes, after prolonged effort at a lower work rate. This, together with the striking persistence of the orthostatic hypotension for long periods after cessation of work may be of significance to clinical medicine in an understanding of the collapse states, and even death, which are encountered after physical effort.⁴ If healthy, young men can develop circulatory failure while erect after exercise, one may guess that similar circulatory changes are not only likely in the older age groups, but that they may be more readily induced, more severe in their manifestations and capable of serious consequences. The effects of physical effort in the older age groups, and the relationship of the changes thereby induced to subsequent disability appears to be a fertile field for study.

Summary. 1. Orthostatic hypotension developed in approximately one-half of normal young men following vigorous exercise of the lower extremities. It followed prolonged moderate work as well as acute exhausting effort.

2. In one-half of those who developed orthostatic hypotension (one-fourth of all subjects) the hypotension was so severe that syncope resulted.

3. The orthostatic hypotension often persists for long periods, over 1 hour, after cessation of the inducing physical effort.

4. The causative factor appears to be a pooling of blood in the dependent lower extremities, presumably due to failure of the muscular venopressor mechanism in the legs, plus a work induced dilatation of their vascular beds.

5. During the orthostatic hypotension, maneuvers which move blood out of the lower extremities, or exclude blood from them, relieve the hypotension.

It is a pleasure to acknowledge the assistance of Major Edgar A. Blair, Inf., A.U.S. in these studies and the technical participation of Tec. 3 Howard Golden and Tec. 4 Wayland James.

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THE TYROSINASE INHIBITING ACTION OF SERUM FROM NORMAL AND CANCEROUS PATIENTS*

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IN a recent paper, Duboff and Hirshfeld¹ reported studies on the tyrosinase-inhibiting action of the serum of cancer patients. Using a system of crude potato tyrosinase, 0.001 M l-tyrosine, and 0.5 ml. of serum in a phosphate buffer, they determined the rate of color development. They reported that 89% of 140 cases of proven active malignant neoplastic disease showed an inhibition of color development equal to or greater than 15% when compared to controls without serum. In 117 normal subjects only 3, and in 68 cases with miscellaneous clinical conditions other than known cancer only 9 caused an inhibition greater than 15%.

On the basis of these findings, Duboff and Hirshfeld concluded that an inhibition greater than 15% in color development of their tyrosinase system is abnormal, and they discussed the possibility of using the inhibition of tyrosinase activity as a basis for a serodiagnostic test for cancer. In view of its obvious importance, the subject was studied in this laboratory using techniques which, so far as we are aware, were precisely similar (with minor exceptions which are noted) to the techniques used by Duboff and Hirshfeld.

CHEMISTRY OF TYROSINASE ACTION. The reactions of tyrosine in the presence of tyrosinase have been studied by Raper *et al.*^{2,8} and recently reviewed by Nelson and Dawson.⁶ Tyrosine is first oxidized to dihydroxyphenylalanine (DOPA). This step is not reversible. The colorless DOPA is then oxidized to DOPA-quinone.

Reducing substances such as ascorbic acid, glutathione, cysteine and thiouracil^{3,4,7} reduce DOPA-quinone to DOPA and thus block the further oxidation to pink halochrome. In the absence of a reducing agent, the DOPA-quinone is oxidized and undergoes an internal rearrangement to a colorless leukobody. This is then oxidized to a pink quinone, halochrome. Halochrome undergoes an internal rearrangement to a colorless compound and is further oxidized to melanin. Tyrosinase is necessary for the formation of DOPA and hence halochrome but not for the formation of melanin.⁸

Methods. Preparation of Crude Tyrosinase. Two types of potatoes, "new" and "Idaho Russet" potatoes, were used. No difference between their action was observed. They were washed thoroughly in tap water, distilled water and then peeled. The outer part of the potatoes was grated and the mash was squeezed through cheese-cloth. The fluid was centrifuged at 3000 to 3500 r.p.m. for 10 minutes. The supernatant was mixed with celite and then filtered through No. 5 Whatman paper. These procedures were performed in a cold room kept at 4° C. The use of celite as a filter aid was not part of the Duboff-Hirshfeld method. However, control experiments using tyrosinase prepared with and without celite showed no essential difference in their reaction with 3 normal and 3 cancer sera.

Collection of the Serum. Blood was drawn 2 to 3 hours before the experiment. The blood was kept at room temperature for 15 to 30 minutes. The clot was rimmed and

* The work reported in this paper was aided by a special grant from the University of Pennsylvania Hospital.

the tube centrifuged at 3000 r.p.m. for 10 minutes. The serum was pipetted off into a clean tube and kept at 4° C. until used.

Solutions. M/15 sodium phosphate buffer of pH 7 to 7.05 was prepared; 0.001 M l-tyrosine in M/15 phosphate solution was freshly prepared every 4 to 5 days and kept at 4° C. when not used.

Preparation of Potato Tyrosinase for Standard Test. Five ml. of 0.001 M l-tyrosine, 0.5 ml. of phosphate buffer and 0.5 ml. of potato juice filtrate were mixed in a Klett-Summerson tube and stirred with a footed stirrer. A reading was made immediately in a Klett-Summerson photoelectric colorimeter (green filter No. 54). Fifteen minutes later, another reading was made. The potato juice was then diluted with buffer to the tyrosinase activity recommended by Duboff and Hirshfeld *viz.* one which produces a color development giving a change of about 0.6 Klett scale units per minute.

Determination of the Activity of Tyrosinase-tyrosine System in the Presence of Serum. Three pairs of Klett colorimeter tubes were set up as follows:

Pair No.	Constant Components
1 . .	5 0 ml. 0.001 M l-tyrosine 0 5 ml. standard potato juice
2 . .	Same as 1
3 . .	Same as 1
	Variable Components
1 . .	0 5 ml. phosphate buffer
2 . .	0 5 ml. normal serum
3 . .	0 5 ml. cancerous serum

The tubes were examined *sciatim* as follows: The serum or phosphate buffer was added to the tyrosine and was immediately followed by the standardized potato juice. The mixture was stirred and read (usually within 0.5 minute) in the colorimeter. Readings were made every 2 minutes for 5 readings and then every 5 minutes for a total of 30 minutes, the times being noted to the nearest 10 seconds.

In the early part of the investigation, the solutions were mixed in the dark and

immediately placed in an illuminated bath for color development in accordance with the original description of Duboff and Hirshfeld. Later this operation was discontinued as unnecessary, an experience in accord with that of Duboff and Hirshfeld (personal communication).

Calculation of Tyrosinase Activity. The changes of the scale readings of the colorimeter were plotted against time. The resultant curve usually showed characteristics illustrated in Figure 1, *viz.*, (1) a *lag phase* during the initial 8 to 12 minutes. This is characterized by either no change in reading or a decrease indicating a diminution of the color, which was always initially present in the reaction mixture. (2) An *activity phase* characterized by a rectilinear change in colorimetric readings indicating constant rate of color production.

On the basis of these curves, the inhibition of tyrosinase activity was calculated by 3 methods: (1) That of Duboff and Hirshfeld. The time at which the *control* tube showed an increase of color of 12 Klett scale units was noted. The increase of reading (R) in the *serum containing tubes* at this time was also recorded. The percentage inhibition was calculated as follows:

$$100 \times \frac{R - 12}{12}$$

By this convention inhibition is negative in sign. (2) The second datum was the *lag phase*, *i. e.*, time between the initial reading and the *beginning* of the constant increase in color formation. As a rule this could be estimated within 1 minute. (3) The *activity phase* was quantitated by calculating the activity of color development from the slope of the line in colorimetric scale units per minute. The result was expressed in percentage increase or decrease from the rate of the control tube without serum, *viz.*,

$$\frac{\text{Activity in the serum tube}}{\text{Activity in the control tube}} \times 100$$

Results. The sera of 24 cases of neoplastic disease and of 24 non-cancerous controls were examined. The diagnosis of neoplastic disease was established beyond

reasonable doubt in each case by either biopsy, operative report, or autopsy in addition to the clinical findings. The non-cancerous cases were patients suffering from miscellaneous ailments which had been definitely diagnosed as non-cancerous. In addition a number of normal subjects were tested.

The data are given in Table 1. In most cases duplicate determinations were done and the mean values were used for the purposes of the summary. Statistical calculation of the means \pm the standard error of the means for both series shows that there is no significant difference between the two.

scale units. In the determination of the inhibition, this error in the initial reading is equivalent to an error of $\pm 16\%$. This conclusion is borne out by a calculation from the data of the entire series of the standard error of the mean of duplicate determinations on a single serum. For Method 1 (see table) it is about 15% and for Method 3 it is 7%. The latter method is somewhat more reliable, but both would require differences of 20 to 45% of inhibition between 2 sera to exist before any significance could be attached to the difference.

Another series of 13 cancer and 18 non-cancerous sera were examined using 2

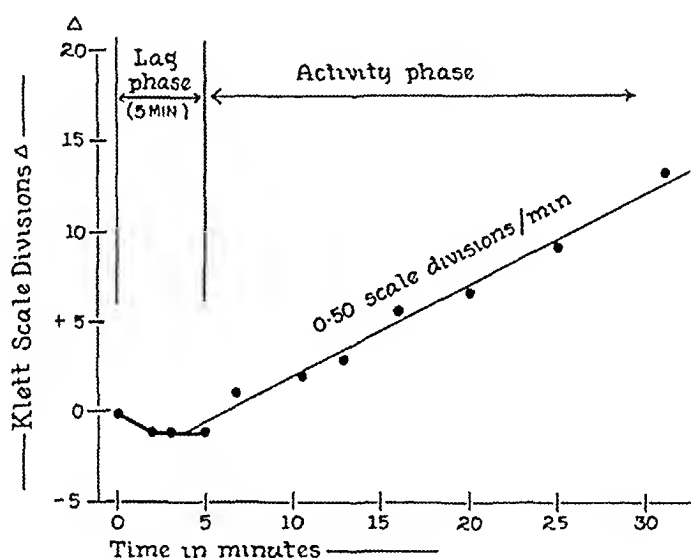


FIG. 1. Typical curve of color development in a tyrosinase-tyrosine serum system showing (a) lag phase and (b) activity phase.

Method 1, that advocated by Duboff and Hirshfeld for the measurement of tyrosinase activity, suffers from a serious technical difficulty. During the initial 2 to 4 minutes of the lag phase, rapid decrease of the intensity of color, as measured by the Klett colorimeter, was frequently observed. This abrupt change of the color intensity was noted in the tubes containing buffer as well as those with sera. Hence this decrease in color could not be attributed solely to a constituent of the sera. Because of the rapidly changing color intensity, the initial reading was not considered reliable to within ± 2 Klett

modifications: (1) The initial reading was taken 10 minutes after the components of the system had been mixed. (2) Potato juice of varying tyrosinase activity was used. The inhibition exceeded 15% in 5 of the 13 cancer sera and in 5 of the 18 non-cancerous sera. Method 3 was used in these calculations. The results are presented in Table 2. Variations in the strength of the potato juice did not significantly alter the inhibition. In this series, as in the first series, there is no significant difference between the cancerous and the non-cancerous sera with

respect to tyrosinase inhibition, as shown by inspection and statistical analysis.

Discussion. The application of simple statistical methods to the evaluation of the data in both of these series of cases

shows that there is no relation between the inhibition by serum of the tyrosinase activity as measured by any of the 3 methods outlined and the cancerous state. We have no explanation for the striking

TABLE 1.—TYROSINE INHIBITION BY CANCEROUS AND NON-CANCEROUS SERA

Type of case	Method 1 (%)	Method 2 (min.)	Method 3 (%)
Cancer:			
Tongue	-16, -42	2, 4	-42, +17
	-33, -58	0, 8	-22, -32
Lip	+12, -12	8, 6	-14, -10
Colon	+8, -4	4, 4	+11, 0
Rectum	+8	0	-7
	-42, +8	4, 3	-10, +8
Uterus	-8, +8	2, 4	-10, -8
Cervix	-17, -8	2, 2	0, -12
	-16, -4	6, 8	-3, -17
Bladder	-12, +8	4, 0	-4, 0
	+20, -8	0, 6	+40, +33
	-35, -30	3, 3	-15, -13
Urethra	-50, -54	8, 6	+11, -10
Prostate	-25	8	-11
Kidney	0, 0	9, 0	-13, -18
Lung	0, -13	3, 4	+5, 0
	-8, +8	0, 5	-24, -19
	-17, -25	5, 10	-25, -14
	-8, -25	2, 2	-24, -27
Breast	+8, -33	1, 2	-4, -4
	+4, -4	2, 4	0, +8
	-8, +8	0, 2	-11, -18
Leukemia:			
Myeloid	-25, -25	4, 3	-7, 0
Lymphoid	0, -33	0, 2	-5, -2
Mean	-13.4 ± 3.3 (S.E.M.)	4.2 ± 0.6 (S.E.M.)	-7.1 ± 2.7 (S.E.M.)
Non-cancer:			
Normal	-70, -50	4, 2	-26, -20
Cyst of neck	-46, -33	3, 2	-17, -8
Arthritis	0, -4	2, 4	+3, 0
Syphilis	+16, +8	2, 2	-17, -12
Thrombocytopenia	-42, 0	7, 6	-15, -3
Coronary thrombosis	+17, +25	4, 3	0, -13
Arteriosclerosis	+8, +25	10, 4	0, 0
Appendicitis	-25, +33	0, 0	-7, +6
Ulcerative colitis	-25	0	-33
Hepatitis	-37, -16	3, 4	-7, -12
Cholecystitis	-12, -29	4, 5	-12, -11
Cholelithiasis	-25, -46	5, 4	-16, -33
Urethral stricture	-29	0	+18
Prostatic hypert. . . .	-35, -38	0, 15	-36, -20
Tbc. of scrotum	+4, 0	0, 0	+10, -8
Tbc. of bone	-46, +21	0, 6	-14, -14
Hernia	-75, -46	3, 5	-43, -44
	-38, -46	7, 12	-17, -8
Cystocele	-58, -12	2, 0	-10, -33
	-16, +12	2, 0	-16, -14
Cervicitis	-8, -8	4, 2	-10, -8
	-4, -33	0, 4	-17, 0
	-29, -8	2, 2	-18, -16
Fracture	+75, +42	0, 0	+44, +20
Mean	-16.3 ± 5.4 (S.E.M.)	3.0 ± 0.5 (S.E.M.)	-11.0 ± 3.2 (S.E.M.)

Standard error, duplicate determinations: Method 1, 14%; Method 3, 7%.

disparity between our results and those of Duboff and Hirshfeld.

However, it was found that some sera did alter the tyrosinase activity of the system in 2 respects: (1) an increase, though very variable, in the time of the *lag phase*, and (2) a decrease, sometimes large, of the rate of color production during the *active phase*. In an attempt to obtain information about these aspects some experiments were done, initiated by the observations of Nelson and Dawson.⁶ They reported that in a tyrosinase-tyrosine system containing ascorbic acid the DOPA quinone formed was reduced as

1 μM of glutathione decolorizes the customary pink initial color of the potato tyrosinase and in addition prevented new color formation for over an hour. With 0.5 μM of ascorbic acid or 0.05 μM of glutathione a more limited cessation of color formation was observed. After a delay period of about 20 minutes, the color formation started abruptly and its rate usually *exceeded* that of the control. It was observed, however, that 0.1 μM of ascorbic acid had no influence on the tyrosinase-tyrosine system. This is the amount roughly equal to the average amount of ascorbic acid in the 0.5 ml. of

TABLE 2.—TYROSINASE INHIBITION BY CANCEROUS AND NON-CANCEROUS SERA (METHOD 3)

Type of case	% change from control rate (activity phase)	Type of case	% change from control rate (activity phase)
Cancer of:		Normal	-11
Face	-7		-11
Tongue	-18		-7
Palate	-12		-7
Stomach	-20		-14
	-15		-11
Liver	-10		-19
Rectum	-22		-24
Bladder	0		-12
Prostate	-8		-13
Lung	-16	Simple fracture	-8
	-12	Infected finger	-12
Mediastinal sarcoma	-13	Urethral stricture	-20
Hodgkin's disease	-14	Hemorrhoids	-3
		Glaucoma	-10
Mean	-12.8 \pm 1.6 (S.E.M.)	Coronary thrombosis	-18
		Non-toxic goiter	-2
		Fibromyoma uteri	-27
		Mean	-12.7 \pm 1.6 (S.E.M.)

soon as formed by the ascorbic acid. Hence there was no color development. When the ascorbic acid was all oxidized, color development promptly began and continued at a rate comparable to controls to which no ascorbic acid has been added. Glutathione⁴ has also been reported to inhibit tyrosinase activity in a similar fashion.

This phenomenon is paralleled by our observations with serum and it is conceivable that the variations in the lag phase could be explained by assuming variable concentrations of reducing substances in the sera. We observed that the addition of 5 μM of ascorbic acid or

the human serum used for the test. Hence the effective amount of ascorbic acid needed to inhibit the system is greater than the usual blood concentration. Confirmation of this conclusion was obtained in the following experiment. The sera of 2 normal individuals were tested before and after the ingestion of 1 gm. of ascorbic acid. No significant differences were observed in either the lag or activity phase of the preprandial or postprandial sera when tested with the tyrosinase system.

However, 0.05 μM of glutathione added to the assay system did cause a significant increase in the delay phase. The amount

is roughly one-third of that usually found in 0.5 ml. of normal serum.

These experiments suggest the possibility that variations of reducing substances, such as glutathione, might be responsible for the increase in the *delay phase*. But the variations in the *activity phase* remained unexplained, for neither ascorbic acid nor glutathione produced any *decrease*, but rather an increase in this activity of the tyrosine-tyrosinase system.

Summary. 1. The suggested serodiagnostic test for malignancy based upon the tyrosinase inhibiting action of serum from cancerous patients, reported by Duboff and Hirshfeld, was studied.

2. The characteristic effect of serum upon the development of color of a l-tyrosine, potato-tyrosinase system could be divided into 2 parts, viz., a *lag phase* and an *activity phase*. On this basis the effect of serum could be expressed in 3 ways, 1 of which is identical with that used by Duboff and Hirshfeld.

3. No significant differences were observed between the effects of sera from 37 cancerous and 42 non-cancerous subjects on the tyrosinase system, and we conclude that the test has no serodiagnostic value in malignancy. The disparity between our results and those of Duboff and Hirshfeld remain unexplained.

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THE TREATMENT OF SYPHILIS OF THE CENTRAL NERVOUS* SYSTEM WITH PENICILLIN*

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THIS report presents the clinical results, the serologic data and the changes in the spinal fluid in 141 patients with neurosyphilis treated with penicillin. These patients have been followed from 6 to 19 months. The principal factors which are known to influence the treatment of neurosyphilis, such as the duration and severity of the disease, the degree of spinal fluid abnormality, and the dosage of penicillin, are analyzed.

Material and Procedures. All of the 141 patients in this series have been treated and observed in this clinic. Of these, 83 were male and 58 female; 51 were white and 90 were Negro. The diagnoses of these cases at the onset of treatment were:

Acute meningitis	4
Early asymptomatic neurosyphilis . . .	19
Late asymptomatic neurosyphilis . . .	74
Congenital asymptomatic neurosyphilis .	5
Meningovascular syphilis	26
Tabes dorsalis	4
Paresis	7
Optic atrophy	2

The group of patients diagnosed as having meningovascular neurosyphilis consisted chiefly of those with pupillary abnormalities, hemiplegias or cranial nerve lesions. Four of the patients in this group had other manifestations of syphilis, such as transverse myelitis, eighth nerve deafness, and meningomyelitis.

Before beginning treatment, a complete history was taken on each patient and a physical examination, including a neurologic and mental status evaluation, was done. Quantitative serologic tests and spinal fluid examinations were also made at this time. Cell counts on the spinal fluid were done

within an hour after the spinal fluid was taken. Quantitative spinal fluid protein determinations were made by electrophotometric measurement of the turbidity produced on the addition of 4 cc. of 3% sulfosalicylic acid to 1 cc. of spinal fluid. The turbidity reading was then compared with that of a known standard protein solution and the level of the spinal fluid protein was determined. Micro-Kjeldahl determinations of the spinal fluid protein were done as a check on the electrophotometer method in several patients in whom the protein level was elevated one year after treatment. In each of these cases the elevated protein determination of the electrophotometer was confirmed. The Kolmer complement fixation test was done with serial dilutions of spinal fluid from .0312 to .5 cc. Colloidal tests were done with mastic solution. The quantitative Kahn test was used on all blood specimens.

At the onset of treatment, the spinal fluid in 81 of the 141 patients in this series showed a definite increase in both cells and protein, in addition to a positive Wassermann reaction. In these 81 cases, the cell count was greater than 10 per cu. mm., the protein more than 45 mgm. %, and the Kolmer was usually positive with less than .25 cc. of spinal fluid. This type of fluid conforms with the Group 3 classification of Moore.⁴ The spinal fluids of 54 patients showed an elevation of *either* cells *or* protein, in addition to a positive Wassermann, and these were classified as Group 2. The remaining 6 patients had inactive Group 2 fluids with a positive

* The penicillin was provided by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for clinical investigations recommended by the Committee on Chemotherapeutic and Other Agents of the National Research Council.

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Wassermann, but with normal cells, protein and mastic.

At the beginning of this study, a total dose of 1.2 million units of penicillin was used in each patient. This dose was later increased to 2 to 3 million units. Sodium penicillin was dissolved in isotonic salt solution and given in equally divided doses intramuscularly every 3 hours. At present, we are using a total dose of 4 million units of penicillin in doses of 50,000 units every 3 hours for 80 injections in 10 days. Cases of primary optic atrophy and general paresis are now receiving a total dose of 6 million units in 18 days. Penicillin is administered in these patients in gradually increasing amounts for the first 3 days to minimize the intensity of the Herxheimer reaction, and then in doses of 50,000 units every 3 hours for the following 15 days. In this paper only the results of one course of penicillin therapy are considered. Each patient was instructed to return at three-month intervals for further physical examinations and for serologic and spinal fluid studies.

Seventy-seven patients were followed for 6 to 8 months, 35 patients from 9 to 11 months, while the remaining 29 patients were followed for 12 to 19 months.

Results. CHANGES IN SPINAL FLUID FOLLOWING TREATMENT. The response of the spinal fluid to penicillin therapy has been classified as follows:

1. *Return to Normal.* This indicates that a complete reversal of the spinal fluid has occurred with the cell count below 10 per cu. mm., the protein level below 45 mgm. %, the mastic reading less than 111000, and the Kolmer reaction negative with .5 cc. of spinal fluid.

2. *Satisfactory Response.* This group includes those spinal fluids in which the cells, protein and mastic have become normal, but the Wassermann reaction remains positive, usually with a decrease in titer. This series of changes probably represents an inactive neurosyphilitic process and we regard it as a satisfactory response to treatment. (Dattner²).

3. *Improved.* This group of cases includes those spinal fluids in which the cell count has become normal, but the protein level remains above 45 mgm. %. The mastic in this group of cases is often greater than 111000, and the Wassermann reaction is always positive, although usually decreased in titer. The protein in most of the patients in this group had fallen from a much higher level, but in a few instances it had remained stationary.

4. *Evidence of Relapse.* Examination of the spinal fluid in this group of patients showed a significant elevation of the cell count (usually 50 cells or more per cu. mm.) 6 months after treatment, indicating that an active neurosyphilitic process existed and that treatment had failed. These patients usually had a normal or decreased cell count 3 months following treatment, but there was a significant rise in cells at the end of 6 months. In an occasional patient, the spinal fluid contained 10 to 20 cells per cu. mm. 6 months following therapy. This was not regarded as evidence of relapse if the cell count had been steadily decreasing. If, however, the cell count remained above 10 per cu. mm. 1 year after treatment was completed, the patient was regarded as a treatment failure and was re-treated.

CHANGES IN SPINAL FLUID IN RELATION TO DOSAGE OF PENICILLIN. Table 1 shows the effect of penicillin therapy on the spinal fluid findings in relation to total dose of penicillin received. In this study, the use of 4 million units of penicillin was the most recently employed dosage schedule. Consequently, the period of follow-up observation in these patients is not as long as in those receiving smaller doses. This factor is of great importance and must be considered in comparing the effects of the various doses of penicillin.

It will be observed that 4 of the 10 patients who received doses of 1.2 million units of penicillin developed evidence of relapse. One patient obtained a normal spinal fluid, while the remaining 5 cases had a satisfactory response. The time the relapses appeared is classified in Table 2

according to the dosage of penicillin and the number of patients under observation. Three of the 4 patients who relapsed following 1.2 million units of penicillin had a significant pleocytosis in the spinal fluid 6 months following treatment, while the remaining patient had a slightly elevated cell count at the end of 1 year.

the large number of normal spinal fluids obtained with this dose.

Although more relapses occurred in patients receiving smaller doses of penicillin, the differences in the period of follow-up observation must be considered. None of the patients receiving 4 million units of penicillin were followed for as long

TABLE 1.—CHANGES IN SPINAL FLUID IN RELATION TO DOSAGE OF PENICILLIN
Spinal Fluid Response

Dose of Penicillin in Million Units*	Number of Patients	Relapsed	Normal	Satisfactory	Improved
1.2	10	4	1	5	..
2.0 to 3.0	63†	7	6	32	18
4.0	63	2	9	34	18

* Three patients with paresis treated with 6 million units are not included. Likewise, 2 children with late congenital neurosyphilis treated with 40,000 units per kilogram of body weight are omitted.

† Of these patients 45 were treated with 2.4 million units.

TABLE 2.—RELATION OF THE TIME OF OCCURRENCE OF SPINAL FLUID RELAPSE TO DOSAGE OF PENICILLIN AND NUMBER OF CASES OBSERVED

Dosage of Penicillin (million units)		Months After Treatment		
		6-8	9-11	12-19
1.2	No. patients under observation.	10	7	6
	No. patients relapsing at specified time	3	..	1
2.0-3.0	No. patients under observation.	63	41	22
	No. patients relapsing at specified time	4	1	2
4.0	No. patients under observation.	63	15	..
	No. patients relapsing at specified time	2

Sixty-three patients received between 2 and 3 million units of penicillin. Of these 7 relapsed, 6 obtained normal spinal fluids, while the remaining improved or had a satisfactory response (Table 1). Of the 7 patients who developed a relapse, 1 had received 2.0 million, 3 had received 3.0 million, and 3 others, 2.4 million units of penicillin. Four of the 7 relapses appeared 6 months after treatment, 1 at 9 months, while the remaining 2 cases were regarded as relapses only at the end of 1 year (Table 2).

Of the 63 patients receiving 4 million units, 2 relapsed, 9 obtained normal spinal fluids, while the remaining cases obtained satisfactory results or improved. Both of the relapses in this group occurred 6 months following treatment.

The patients treated with the various doses of penicillin were in general comparable as to the type of neurosyphilis. There were, however, more patients with early neurosyphilis treated with 4 million units of penicillin than with smaller doses. This would account to some extent for

as a year, and relatively few of this group have been observed longer than 9 months. All of the patients in this study, however, have been observed for at least 6 months following treatment and a comparison of the relapses occurring at this period of time is shown in Table 2. Although the number of patients treated with 1.2 million units of penicillin is small, the appearance of spinal fluid relapses six months after treatment in almost one-third of these cases indicates that this dosage is inadequate. In the two groups of patients treated with 2 to 4 million units, the number of relapses occurring 6 months after treatment was not significantly different. It is our belief, however, that doses of penicillin less than 4 million units will prove to be unsatisfactory in the treatment of neurosyphilis and should not be used in this condition.

RELATION OF SPINAL FLUID CHANGES TO DURATION OF DISEASE. Table 3 shows the changes in the spinal fluid classified according to the duration of the disease. It will be noted that approxi-

mately one-half of the patients known to have early neurosyphilis (less than 5 years' duration) developed a normal spinal fluid, whereas only 6 of the 118 patients who appeared to have late syphilis obtained a reversal of the spinal fluid. Likewise, there were many more spinal fluid relapses in the late cases of neurosyphilis.

of 211000, and a positive Wassermann with .0625 cc. of spinal fluid. This patient had no clinical evidence of neurosyphilis. He was given 4 million units of penicillin and 6 months later his spinal fluid showed 165 cells, 54 mgm. % of protein, with no change in the Wassermann or mastie reactions. His lack of response to penicillin is interesting in view of his failure to

TABLE 3.—RELATION OF SPINAL FLUID CHANGES TO DURATION OF DISEASE

Duration of Infection	Number of Patients	Spinal Fluid Response			
		Relapsed	Normal	Satisfactory	Improved
Early neurosyphilis	23*	1	10	12	
Late neurosyphilis†	118	12	6	62	35

* Eighteen of these patients were treated with 4 million units of penicillin.

† These cases included those of unknown duration, presumed to be more than five years.

TABLE 4.—RELATION OF SPINAL FLUID CHANGE TO FINDINGS IN THE FLUID PRIOR TO TREATMENT

Findings in Spinal Fluid Before Treatment	Number of Patients	Spinal Fluid Response			
		Relapsed*	Normal	Satisfactory	Improved
Inactive Group II	6		1	5	
Group II	51	4	9	33	8
Group III	81	5†	6	36	30

* Six months after treatment.

† Four additional patients with Group 3 spinal fluid findings showed evidence of relapse later than 6 months following treatment.

None of the patients with early neurosyphilis had initial primary or secondary syphilitic manifestations; the duration of the infection in these cases was usually 2 to 3 years. Several of them had relapsing cutaneous manifestations, but most of them had an asymptomatic neurorecurrence or meningitis.

The good results obtained with the use of penicillin in the treatment of early neurosyphilis has also been noted by others. Nelson⁵ reported clinical cure and spinal fluid reversals in a number of patients with acute meningitis treated with penicillin, while O'Leary⁶ states that penicillin therapy was most promising in the treatment of the meningeal form of this condition.

The 1 patient in this series with early neurosyphilis who developed a spinal fluid relapse was a 21 year old white man who had a penile lesion 3 years previous to his penicillin therapy. Despite almost 3 years of continuous and regular arsenical and bismuth treatments at various prison camps, this patient's spinal fluid showed 98 cells, 30 mgm. % of protein, a mastie

respond to adequate treatment with arsenic and bismuth.

RELATION OF SPINAL FLUID FINDINGS BEFORE TREATMENT TO THE CHANGES FOLLOWING PENICILLIN The response of the spinal fluid to penicillin therapy is classified in Table 4 according to the findings in the fluid immediately prior to treatment.

Most of the patients treated early in this study had Group 3 spinal fluids. This group of patients therefore have the longest period of follow-up observation and have also received the smaller doses of penicillin. These two factors must be considered in comparing the results obtained with Group 2 and Group 3 spinal fluids.

Approximately the same number of relapses occurred six months after treatment in patients with Group 2 and Group 3 fluids. There were, however, more patients in Group 2 developing normal spinal fluids than in Group 3. Although these findings may be the result of differences in dosage, it is nevertheless our impression that patients having maximal

spinal fluid changes obtained less satisfactory results following penicillin therapy.

Only one of the patients in this series with inactive Group 2 spinal fluids (those with normal cells, protein and mastie, but with a positive Wassermann) obtained any significant change in his spinal fluid findings, and this was a case of early neurosyphilis. In late cases of syphilis, this type of spinal fluid represents an inactive neurosyphilitic process (Dattner²). We think it probable that little or no change in the spinal fluid can be expected in these cases following penicillin therapy.

There were 38 patients in this entire series who were classified as improved and showed normal cell counts following treatment, but had persistently elevated spinal fluid proteins and positive Wassermann reactions. These cases are of considerable interest. Many of these patients have had a significant decrease in the spinal fluid protein and their present level is only slightly higher than 45 mgm. %. Since the elevation of the protein is usually much slower to subside than the pleocytosis, these patients cannot be called treatment failures at this time.

There were, however, 12 patients who had an increase in spinal fluid protein at the onset of treatment who still show an appreciable elevation in protein (more than 60 mgm. %) despite penicillin therapy. Three of these patients had normal cell counts before treatment. Significantly, all of these cases had syphilis of long duration, and one-half of them had either meningovascular syphilis or had definite parenchymatous involvement, such as paresis or tabes. Elevation of the spinal fluid protein in such cases has been found to persist for as long as 4 years or more following fever therapy.^{2,3} It has been observed, moreover, that paretics with very high spinal fluid proteins show considerable tendency to maintain such levels almost continuously following fever therapy and that the clinical results in these patients are no different from those with low spinal fluid proteins.⁵ In meningitis and in early neurosyphilis, however,

we have observed a rapid and dramatic fall of extremely high protein levels following penicillin or arsenicals. The persistence of a high protein in the spinal fluid in our patients may therefore represent a severe degree of destruction in the central nervous system and does not necessarily indicate that penicillin was ineffective. It is this group of cases, however, that needs most prolonged and careful observation before the value of penicillin can be accurately assessed. Some of them probably will become treatment failures.

RELATION OF SPINAL FLUID RESPONSE TO BLOOD SEROLOGIC TESTS. No apparent relation was noted between the results obtained in the spinal fluid and those obtained in blood serologic tests (Table 5).

None of the patients who developed a relapse in spinal fluid showed a rise in the titer of the quantitative Kahn. The Kahn titer fell in 7 of these cases, but remained the same in 5 others. None of these patients developed a negative blood serologic test.

Of the 16 patients who developed a normal spinal fluid, only 8 obtained a negative serologic reaction. The majority of the patients in this study showed a decrease in the titer of the blood serologic test regardless of the spinal fluid response. In many of the patients, however, no change in blood titer was noted, despite a satisfactory response or improvement in the spinal fluid.

The lack of correlation between blood and spinal fluid findings following penicillin therapy is noteworthy. It is easily understood how patients with relapsing neurosyphilis can be overlooked if one relies entirely upon the blood serologic test. In this study the majority of patients with evidence of neurorelapse showed no clinical symptoms, and in such cases, failure to respond to treatment can only be diagnosed early by repeated examinations of the spinal fluid.

RELATION OF SPINAL FLUID RESPONSE TO TYPE OF NEUROSYPHILIS. As suggested in the foregoing paragraphs, the types of

neurosyphilis that seemed to respond best to penicillin therapy were those with early asymptomatic neurosyphilis or acute syphilitic meningitis. This group of cases obtained the greatest number of normal spinal fluids and developed the smallest number of relapses (Table 6).

All but 1 of the 5 patients with late congenital asymptomatic neurosyphilis obtained a satisfactory spinal fluid response. This patient had 200 mgm. % of protein in the spinal fluid and no cells prior to treatment, and 11 months later showed only a slight reduction in the spinal fluid protein.

icillin is poorest in the more advanced cases of neurosyphilis.

The large number of patients with parenchymal neurosyphilis who maintain an elevation of the spinal fluid protein has been mentioned previously in this report. Since this group of patients have most destruction of the central nervous system, and since the ultimate response of such spinal fluids to penicillin is not known, the importance of prolonged observation of this particular group of patients is again emphasized.

THE RELATION OF SPINAL FLUID RESPONSE TO PREVIOUS TREATMENT.

TABLE 5.—RELATION OF SPINAL FLUID RESPONSE TO BLOOD SEROLOGIC TESTS

Results of Serologic Tests of Blood	Number of Patients*	Spinal Fluid Response			
		Relapsed	Normal	Satisfactory	Improved
Became negative	31*		8	18	8
Decreased in titer	58	7	7	33	11
No change	16	5	1	21	19
Increased in titer					

* Of these patients 12 had negative or doubtful blood serologic tests at onset of therapy.

TABLE 6.—RELATION OF SPINAL FLUID RESPONSE TO TYPE OF NEUROSYPHILIS

Diagnosis at Onset of Therapy	Number of Patients	Relapsed	Spinal Fluid Response		
			Normal*	Satisfactory	Improved
Acute meningitis	4		2	2	
Early asymptomatic	19	1	8	10	
Congenital asymptomatic	5			4	1
Late asymptomatic	74	10	6	41	17
Meningovascular	26	2		15	9
Tabes	4				4
Optic atrophy	2			2	
Paresis	7				7

* Of these patients 5 have a doubtful or a 2-plus Kolmer reaction with 0.5 cc. of spinal fluid.

Seventy-four patients in this series appeared to have late asymptomatic neurosyphilis. Most of these responded well to treatment and obtained satisfactory or normal spinal fluids. Ten of them relapsed, however, and 17 others maintained elevated spinal fluid proteins.

None of the patients with meningovascular neurosyphilis, paresis, tabes or optic atrophy obtained normal spinal fluids. Less than one-half of them showed a satisfactory response, and many of them showed persistently elevated proteins. These findings are in general in accordance with those noted by others⁷ and demonstrate that the spinal fluid response to pen-

The therapy our patients received prior to penicillin treatment has been classified into 4 groups: (1) No treatment; (2) poor chemotherapy, consisting of less than 25 arsenic and 25 bismuth injections; (3) adequate chemotherapy, consisting of more than 25 arsenic and 25 bismuth injections, regardless of the regularity and time over which it was given; (4) fever therapy.

There did not appear to be any correlation between the failure of the spinal fluid to respond to penicillin and the amount of previous treatment. Of the 13 cases who developed evidence of relapse, 3 had had no previous therapy;

2, poor therapy; 7, adequate therapy, and 1 had had fever.

The effects of previous therapy, however, cannot be accurately evaluated. Greater amounts of treatment, including fever, were usually given to the more advanced cases, and the results of penicillin in these instances were less satisfactory.

It should be emphasized, however, that approximately one-half of the patients who obtained normal or satisfactory spinal fluid findings had had adequate chemotherapy previously, indicating that penicillin has a far greater effect on syphilis of the central nervous system than routine chemotherapy. This observation is, we believe, of considerable importance and indicates that penicillin should replace entirely the use of routine arsenic and bismuth preparations in the treatment of neurosyphilis.

consists of fifty hours of temperature greater than 103° F., obtained by intravenous infusion of typhoid vaccine in seven to ten courses. In 31 of the 48 patients considered in the table, no further treatment was given following fever therapy. In 17 cases, however, 10 to 20 weekly injections of tryparsamide were given after fever was completed. Since no significant differences could be observed in this small series in the spinal fluid response of those receiving fever alone and those receiving fever and tryparsamide, both groups are considered together for comparison with penicillin-treated patients.

In general, the number of patients obtaining a normal or satisfactory spinal fluid is approximately the same with the two methods of treatment. The number of relapses following fever was not sig-

TABLE 7.—COMPARISON OF THE RESPONSE OF SPINAL FLUID TO PENICILLIN WITH THAT OBTAINED AFTER FEVER THERAPY (TYPHOID VACCINE)

Method of Therapy	Number of Patients*	Spinal Fluid Response			
		Relapsed	Normal	Satisfactory	Improved
Penicillin, 4 0 million units	48	1	1	27	19
Fever therapy*	48	3	2	32	11

* Two of these patients received malaria.

COMPARISON OF RESPONSE OF SPINAL FLUID TO PENICILLIN THERAPY WITH THAT OBTAINED WITH FEVER. During the two years prior to the use of penicillin in this clinic, we had employed fever therapy routinely in the treatment of the same types of neurosyphilis we are now treating with penicillin. The spinal fluid responses of these two methods of therapy are compared in Table 7. Patients with early neurosyphilis are not considered, since fever was rarely used in these cases. Only patients who received at least 4 million units of penicillin are included in this comparison.

Observations of the spinal fluid response in patients treated with fever were usually made 12 to 18 months following therapy. The two groups of cases are otherwise comparable, particularly in regard to diagnosis and initial spinal fluid abnormalities. The course of fever therapy in this clinic

nificantly higher than that obtained with penicillin. It will be noted, however, that more patients maintained an elevated protein after penicillin than after fever, possibly because the period of follow-up observation was longer in patients treated with fever.

Although the response of the spinal fluid to penicillin appears to be equal to that obtained with fever, it must be remembered that clinical improvement does not always parallel the spinal fluid findings. It is extremely difficult to compare any two groups of patients with neurosyphilis in regard to the improvement in clinical symptoms, but it is our impression that the results of fever therapy were somewhat better than penicillin therapy in our patients with paresis. In asymptomatic neurosyphilis, however, or in patients in whom only an arrest in progress

may be expected, penicillin definitely appears to be the treatment of choice.

RESPONSE OF CLINICAL SYMPTOMS TO PENICILLIN THERAPY. The majority of patients in this series were asymptomatic at the onset of treatment or had irreversible meningovascular manifestations, such as fixed pupils and long-standing hemiplegias. It was not possible, therefore, to ascertain any objective clinical improvement following treatment in most of our patients.

There was, however, a surprising number of patients in this series who obtained marked subjective improvement. These patients frequently stated that they felt better, had gained weight, had more pep and vigor and were "one hundred percent different." Many of them also obtained relief from headaches, malaise and muscular aching, although these symptoms were not mentioned by them at the time of their initial examination. Such "tonic" effects have also been noted by others. O'Leary,⁶ for example, found that weight gain was a common occurrence and noted that an over-all general improvement was frequently obtained.

The response of specific symptoms of neurosyphilis to penicillin therapy was, however, considerably more variable. In 2 patients with tabes, ataxia was greatly improved and the patients returned to work. On the other hand, 2 other patients with lightning pains obtained only temporary relief.

Six of the 7 patients with early paresis showed definite improvement and are now well enough to return to their former jobs. The response to penicillin was often very dramatic, with immediate improvement of tremors, handwriting and slurring of speech. One patient, however, showed only slight improvement in mental status. Records have been obtained from 6 other patients with paresis, who are not included in this series, as they were transferred to psychiatric institutions and could not be observed in this clinic. Four died and two remain psychotic. In all of these

cases, however, the disease was far advanced at the onset of treatment.

Both patients with optic atrophy have shown progressive loss of vision and constriction of visual fields, despite the fact that their spinal fluids have responded satisfactorily. The patients with transverse myelitis, meningomyelitis and eighth nerve deafness have not shown any definite clinical improvement.

REACTIONS. The most common reaction encountered in our patients was an initial febrile Herxheimer effect. This usually occurred on the first day of therapy, but was sometimes delayed until the second or third day in those patients who received gradually increasing doses of penicillin. Three of the 7 patients with paresis became considerably agitated at the onset of therapy and had to be restrained, but this effect was only temporary. One patient (not included in this series) who had been diagnosed as asymptomatic before treatment, developed an acute psychosis during penicillin therapy, necessitating discontinuance of therapy. Although such reactions have been previously reported,¹ they are relatively uncommon.

Discussion. Only a relatively small number of patients in this series obtained normal spinal fluids after penicillin. This we believe is due to the comparatively short period of observation which has elapsed following treatment. As pointed out by Stokes and his associates,⁷ there is a striking increase in the number of normal spinal fluids with longer periods of observation. We believe that most of the patients with a satisfactory spinal fluid response and some of those with improvement in the spinal fluid will soon obtain normal findings.

The criterion for relapse in this series has been based entirely upon the cell count, for this is believed to be the most sensitive indication of the activity of the neurosyphilitic process.² In 10 of the 13 patients in this series who relapsed, there appeared to be an initial improvement in the cell count, but approximately six months following therapy, the cells

rose again to the original level or higher. In the remaining 3 cases, the cell count showed a steady decline but was still greater than 10 cells per cu. mm. a year following therapy.

We have found the response of the protein to be considerably slower and not as sensitive as the cell count. The protein rose in only 3 of the 13 patients who showed an increase in cells. Changes in the mastie were generally reflected by the more accurate quantitative protein determinations. No change was noted in the mastie reaction in any of the cases of relapse.

Only marked changes in the Wassermann titer of at least 2 or 3 dilutions were regarded as significant in this study. Minor changes of 1 or 2 dilutions could not be depended upon as an indication of relapse because of the daily uncontrollable laboratory variation in the sensitivity of the complement fixation reaction. In this series, only 5 of the patients with relapse showed any significant changes in the Wassermann titer. As mentioned previously, the blood serologic test was of no value in the detection of relapsing spinal fluids.

Clinical symptoms were also of little importance as an early indication of treatment failure. Only 2 patients with relapsing spinal fluids developed any clinical signs. One of them noted a recurrence of headache, while the other suffered a transient monoplegia. For these reasons, we have come to depend almost entirely on the cell count for re-treatment of our asymptomatic cases, since neither the clinical, serologic, or other spinal fluid findings appeared sufficiently reliable for the early diagnosis of treatment failure.

In several patients there was a return or progression of symptoms, despite a satisfactory response or improvement in their spinal fluids. The decision to give further treatment to these patients depended upon the type and severity of their symptoms.

Patients who showed a relapse in the spinal fluid following small doses of peni-

cillin were re-treated with 6 million units of penicillin. Those relapsing after large amounts of penicillin were given fever therapy, in addition to twice the original amount of penicillin.

In one of the patients in this series, the cell count was normal at 3 and 6 months, but increased 9 months following therapy. It appears therefore that, although most relapses occur within the first 6 months, patients treated with penicillin should be followed for considerably longer intervals. A somewhat greater relapse rate is to be expected in this series, therefore, with longer periods of observation. (See Addendum).

The total number of spinal fluid relapses, however, in this group of patients with neurosyphilis who received 4 million units of penicillin will be quite small and will probably be less than 15%. Penicillin is a very valuable agent in the treatment of this condition and should replace arsenic and bismuth preparations. Moreover, in asymptomatic neurosyphilis it is an effective and a safer method of treatment than fever. We believe that fever therapy is still the method of choice in most of the patients with late symptomatic neurosyphilis. The frequent and dramatic response of many of these cases to penicillin, however, and the safety of this form of therapy make the use of penicillin warranted in earlier and milder forms of this condition.

Conclusion. One hundred and forty-one patients with syphilis of the central nervous system were treated with doses of penicillin ranging from 1.2 to 6 million units and were followed for 6 to 19 months. Our results are in general similar to those reported by others and penicillin appears to be an effective agent in the treatment of this condition.

Preliminary observations on the use of 4 million units of penicillin indicate that this dosage will probably produce an arrest of the neurosyphilitic process in more than 85% of the cases.

Patients with early neurosyphilis obtain a better response to penicillin than late

cases. It is our impression that the results in patients with maximal spinal fluid findings in late syphilis are not as good as those with less severe spinal fluid findings. Moreover, patients with late symptomatic neurosyphilis seemed to obtain less satisfactory spinal fluid responses than those without symptoms. In general, however, the response of the spinal fluid in late cases of neurosyphilis was as good as that obtained with fever therapy.

No correlation was observed between the changes in the blood serologic tests and the response of spinal fluid following penicillin.

Marked subjective improvement and a sense of well-being were frequently noted in patients with neurosyphilis treated with penicillin. Although the clinical improvement in paresis and tubes was occasionally striking, it did not always parallel the improvement of the spinal fluid in these cases.

The cell count of the spinal fluid was found to be a sensitive index of treatment failure. In those patients developing a relapse after penicillin, a significant elevation in the cell count was usually noted six months after treatment. Occasionally, however, longer periods of observation were necessary before evidence of relapse could be detected. In this study, 13 of 141 patients were found to have evidence of spinal fluid relapse following penicillin therapy. There were, in addition, a small group of patients who developed a recurrence of clinical symptoms or a progression of their neurosyphilitic manifestations following therapy.

Penicillin is recommended for the treat-

ment of early neurosyphilis and late asymptomatic neurosyphilis provided adequate facilities are available for follow-up examinations of the spinal fluid. In late symptomatic neurosyphilis penicillin does not replace fever therapy as the treatment of choice. The safety of penicillin therapy, however, and the frequent dramatic results obtained in these cases warrant the use of penicillin in earlier and milder forms of this condition.

The patients in this study have been followed for only a relatively short period of time, and these conclusions must therefore be regarded as preliminary. The results described in this paper, moreover, must be interpreted in light of the fact that commercial penicillin has been a changing mixture of various substances. The content of impurities has gradually decreased as potency in terms of units per milligram has increased. The relative amounts of the several identified penicillin fractions G, F, X and K, have likewise varied from time to time. These two changes and perhaps others suggest that therapeutic efficacy may not have remained constant, and that it may be significantly different today than it was originally. It is not now possible to assess the extent to which these changes may have affected the results here reported.

Addendum. Since this paper was submitted for publication, evidence of spinal fluid relapse has appeared in 3 of the patients with late neurosyphilis treated with 4 million units of penicillin. Each of these patients showed 17 to 20 cells per c.mm. a year after treatment was completed.

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THE ORAL ADMINISTRATION OF PENICILLIN IN DOGS

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THIS report describes the results of an investigation of the effectiveness of various substances for the protection of orally administered penicillin in dogs. The manner in which various substances protect penicillin against destruction by gastric acidity has been reviewed.¹ Experiments in humans with certain oral penicillin preparations have been reported by Finland *et al.*²

The protective substances for the animal experiments were selected on the basis of their ability to protect penicillin against acid inactivation as indicated by *in vitro* experiments with artificial gastric juice. The protective substances investigated included alkaline buffers, antacids, proteinic materials and oils. Commercial penicillin calcium was used throughout the study.

IN VITRO STUDIES. Measurement of the pH values after the addition of successive portions of soluble, alkaline salts to 25 cc. portions of artificial gastric juice* indicated that certain of these salts were capable of buffering the juice at a pH range compatible with the stability of penicillin. The effect of trisodium citrate, sodium acetate and dibasic sodium phosphate is illustrated in Figure 1. Several other antacids were also found to adjust the pH of the juice to a satisfactory level. The effect of calcium carbonate and tricalcium phosphate are illustrated in Figure 2. It is apparent from Figures 1 and 2 that these substances maintained the pH in a satisfactory range even after the addition of more artificial gastric juice.

Under these conditions penicillin was protected against rapid destruction.

The protective effect of certain buffers and antacids was demonstrated in the following experiments. In artificial gastric juice to which no buffers or antacids were added, 20,000 units of penicillin calcium was completely inactivated after incubation at 37.5° C. for 30 minutes. In samples of artificial gastric juice containing 20,000 units of penicillin calcium and 750 mg. of disodium phosphate, sodium acetate or trisodium citrate respectively, 80% of the drug was present after incubation at 37.5° C. for 30 minutes. A similar protective effect was observed when 500 mg. of calcium carbonate or tricalcium phosphate was used.

Several protein materials, including soluble egg albumen, skimmed milk powder and whey powder were ineffective in raising the pH of artificial gastric juice to a range compatible with penicillin stability. Nevertheless, under certain conditions, these substances protected penicillin against acid inactivation. A control solution buffered to pH 3, containing 100 units of penicillin per cc., lost 25% of its activity during incubation for 50 minutes at 24° C. On the other hand, similar solutions containing 2% of skimmed milk powder, soluble egg albumen or whey powder required 4 hours at 24° C. for the same degree of inactivation.

Cottonseed oil had no protective effect upon penicillin. Incubation of 1 cc. of a suspension of 100,000 units of penicillin calcium in cottonseed oil with 25 cc. of

* Hydrochloric acid (36%)	16 3 cc.
Sodium chloride	9 0 gm.
Disodium phosphate	2 0 gm.
Pepsin	5 0 gm.

Lactic acid	1 gm.
Amino-acetic acid	1 gm.
Distilled water, q.s.	1000 cc.

artificial gastric juice resulted in complete inactivation of the penicillin within 30 minutes. The use of a soft elastic gelatin capsule to enclose the penicillin-oil suspension offered no protection to the drug under similar conditions.

IN VIVO STUDIES. Mongrel dogs, weighing 8 to 10 kg., were used in this investigation. Their diet consisted of single daily feedings of chopped horse meat, Gaines dog meal and milk. Water was available at all times. During an experiment the

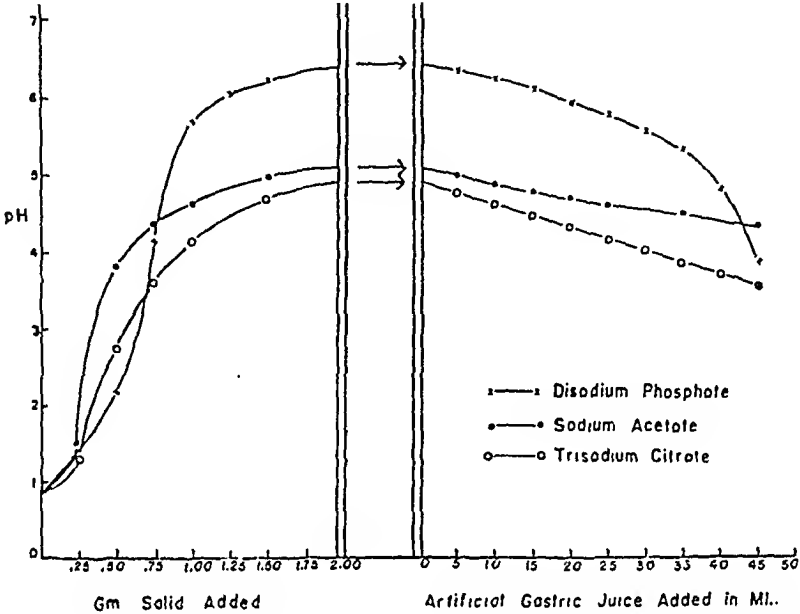


FIG. 1.—pH of artificial gastric juice following addition of various soluble alkaline salts.

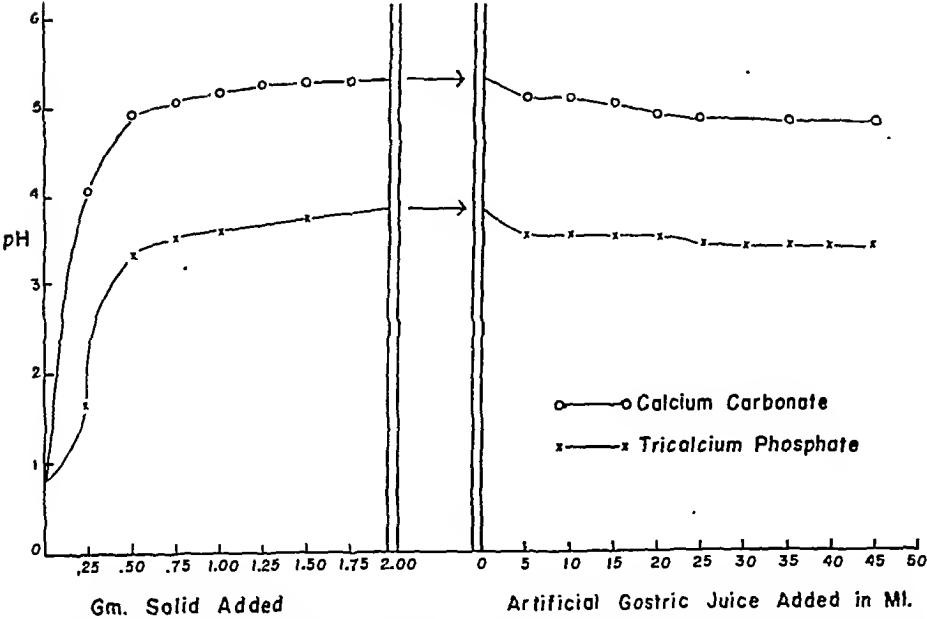


FIG. 2.—pH of artificial gastric juice following addition of calcium carbonate and tricalcium phosphate.

dogs were kept in large metabolism cages in an air-conditioned room. The animals were fasted for 12 hours before the experiment. Prior to penicillin administration and again at the 4th hour, each animal was given 200 cc. of water by stomach tube to insure adequate urine flow.

Unless otherwise stated, penicillin calcium was administered orally in the form of compressed tablets with the protective substances as a component part. The tablets were given in single doses of 100,000 units or by repeated administration comprising an initial dose of 30,000 units and 10,000 units hourly thereafter until a total of 100,000 units was given. Penicillin calcium in oil suspension was administered orally in the form of soft elastic gelatin capsules in single doses of 100,000 units.

Serum and urine samples, taken at hourly intervals during the experiment, were assayed by a modification of the cup-plate method.³ The minimum concentration of penicillin in the serum measured quantitatively by this test was 0.2 unit per cc.

BUFFERS AND ANTACIDS. In preliminary experiments each of 3 groups of dogs was pre-conditioned by the oral administration of soluble buffering salts dissolved in water in the following amounts, respectively: disodium phosphate, 6 gm.; sodium acetate, 6.5 gm.; trisodium citrate, 5 gm. Thirty minutes later 100,000 units of penicillin calcium in water was given with the following amounts of buffers, respectively: disodium phosphate, 5 gm.; sodium acetate, 3.5 gm.; trisodium citrate, 5 gm. One group of control animals without pre-conditioning received 10 gm. of lactose and 100,000 units of penicillin calcium dissolved in water. Another group received an aqueous solution of 100,000 units of penicillin calcium alone. In a second series of experiments, pre-conditioning of the animals was omitted. The penicillin and soluble buffering salts or antacids were administered in the same tablet according to the single and repeated dosage schedules outlined above. Control

animals received penicillin calcium alone.

The data presented in Tables 1 and 2 indicate that oral pre-conditioning of dogs with soluble alkaline buffering salts offered no advantage over the simultaneous administration of penicillin and the buffering substance. On the other hand, the data in Table 3 indicate that repeated oral administration of soluble buffering salts or antacids in combination with penicillin resulted in high levels of penicillin in the sera of dogs. These levels were maintained as long as the administration of penicillin was continued. A mild diarrhea was observed after repeated administration of disodium phosphate, thereby detracting from the usefulness of this buffer for oral penicillin.

Early appearance of penicillin in the urine followed the rapid disappearance of the drug from the blood stream. Urinary levels ranging from 10 to 50 units per cc. were detected within 30 to 60 minutes after the administration of penicillin in combination with soluble buffers or antacids. The quantity of penicillin excreted in the urine of the dogs after repeated oral administration with such agents was 4 to 6 times that excreted after similar administration of penicillin in water.

PROTEIN SUBSTANCES. Repeated administration of soluble alkaline buffering substances and certain antacids presents the possibility of producing gastric irritation and alkalosis. In order to overcome this potential objection to the use of alkaline substances and antacids, protein materials were explored as protective agents for orally administered penicillin. Although the *in vitro* tests indicated that skimmed milk powder, soluble egg albumen and whey powder all protected penicillin against acid destruction, the urinary excretion data following the single administration of 100,000 units of penicillin with the same amounts of these 3 protein materials showed that the skimmed milk powder was much more efficient in the animal tests than soluble egg albumen or whey powder. A comparison of the data

TABLE 1.—SERUM AND URINARY CONCENTRATIONS OF PENICILLIN FOLLOWING ORAL ADMINISTRATION WITH SOLUBLE ALKALINE BUFFERING SALTS

Protective substance	Single Dose = 100,000 Units (With Pre-treatment)							% urinary excretion 24 hours
	Hourly serum levels (units per cc.)							
	1	2	3	4	5	6	7	
Disodium phosphate	0.2	0.3	0.4	0.3	<0.2	<0.2	..	26.0
Sodium acetate	0.2	0.3	0.4	<0.2	<0.2	<0.2	..	30.4
Trisodium citrate	0.3	0.2	<0.2	<0.2	<0.2	<0.2	..	23.0
Water (control)	1.6	0.7	0	0	0	0	..	4.1

TABLE 2.—SERUM AND URINARY CONCENTRATIONS OF PENICILLIN FOLLOWING ORAL ADMINISTRATION WITH SOLUBLE ALKALINE BUFFERING SALTS AND ANTACIDS

Single Dose = 100,000 Units (Without Pre-treatment)								% urinary excretion 24 hours
Protective substance	Hourly serum levels (units per cc.)							
	1	2	3	4	5	6	7	
Sodium acetate	0.2	<0.2	<0.2	0	0	0	0	15.6
Trisodium citrate	1.6	0.5	0.3	<0.2	<0.2	<0.2	0	22.8
Calcium carbonate	1.4	1.0	0.4	0.3	<0.2	<0.2	<0.2	22.4
Tricalcium phosphate	>2.0	0.7	<0.2	<0.2	<0.2	<0.2	<0.2	26.6
Water (control)	1.6	0.7	0	0	0	0	..	4.1

TABLE 3.—SERUM AND URINARY CONCENTRATIONS OF PENICILLIN FOLLOWING ORAL ADMINISTRATION WITH SOLUBLE ALKALINE BUFFERING SALTS AND ANTACIDS

Repeated Dosage = 30,000 Units Initially and Then 10,000 Units Hourly; 100,000 Units Total								% urinary excretion 24 hours
Protective substance	Hourly serum levels (units per cc.)							
	1	2	3	4	5	6	7	
Sodium acetate	1.2	0.4	0.4	0.7	1.0	0.4	0.5	31.1
Trisodium citrate	1.2	1.4	0.3	0.4	0.5	0.7	1.0	27.7
Calcium carbonate	0.4	0.5	0.8	0.5	1.2	0.5	0.3	46.1
Tricalcium phosphate	0.8	0.6	0.6	1.0	0.4	0.5	0.5	32.7
Water (control)	0.2	0.6	0.5	<0.2	0.3	<0.2		7.3

TABLE 4.—SERUM AND URINARY CONCENTRATIONS OF PENICILLIN FOLLOWING ORAL ADMINISTRATION WITH PROTEINS AND PROTEIN-CONTAINING MIXTURES

Protective substance	Single Dose = 100,000 Units							% urinary excretion 24 hours
	Hourly serum levels (units per cc)							
	1	2	3	4	5	6	7	
Skimmed milk powder	1.2	0.8	0.2	0.2	<0.2	<0.2	<0.2	24.0
Egg albumen powder	1.4	0.4	0.3	0.2	0	0	0	15.6
Whey powder	1.5	0.5	<0.2	0	0	0	0	13.1
Water (control)	1.6	0.7	0	0	0	0		4.1

TABLE 5.—SERUM AND URINARY CONCENTRATIONS OF PENICILLIN FOLLOWING ORAL ADMINISTRATION WITH PROTEINS AND PROTEIN-CONTAINING MIXTURES

Repeated Dosage = 30,000 Units Initially and Then 10,000 Units Hourly; 100,000 Units Total								% urinary excretion 24 hours
Protective substance	Hourly serum levels (units per cc.)							
	1	2	3	4	5	6	7	
Skimmed milk powder	>2.0	0.4	0.4	0.4	0.3	0.2	0.2	20.1
Egg albumen powder	0.0	0.4	0.3	0.3	0.4	0.3	0.2	6.3
Whey powder	1.0	0.6	0.7	0.6	0.6	0.5	0.3	17.1
Water (control)	0.2	0.6	0.5	<0.2	0.3	<0.2	..	7.3

Protective substance	Repeated Dosage = 40,000 Units Initially and Then 10,000 Units Hourly; 90,000 Units Total							% urinary excretion 24 hours
	1	2	3	4	5	6	7	
Skimmed milk powder	2.0	1.4	0.8	0.5	0.7	0.5	..	32.0

TABLE 6.—SERUM AND URINARY CONCENTRATIONS OF PENICILLIN FOLLOWING ORAL ADMINISTRATION OF OIL SUSPENSIONS IN SOFT ELASTIC GELATIN CAPSULES

Single Dose = 100,000 Units							
Protective substance	Hourly serum levels (units per cc.)						% urinary excretion 24 hours
	1	2	3	4	5	6	
Cottonseed oil	0.9	0.5	<0.2	<0.2	<0.2	0	5.0
Linseed-peanut oil	0.5	0.3	<0.2	<0.2	<0.2	0	9.0
Water (control)	1.6	0.7	0	0	0	0	4.1

presented in Tables 2 and 4 indicates that the administration of penicillin with skimmed milk powder in single oral doses produced concentrations of penicillin in the sera and urine of dogs equal to those produced by single doses of penicillin with the buffering substances and antacids. A comparison of the data in Tables 3 and 5 indicates that the repeated administration of penicillin with skimmed milk powder produced concentrations of penicillin in the sera and urine of dogs equal to those produced by the administration of penicillin with buffers and antacids in repeated doses.

No deleterious physiologic effects were observed in the animals receiving combinations of penicillin and these proteinic substances.

OILS. Oil vehicles have been reported⁴ to protect orally administered penicillin against destruction by gastric acidity. In order to evaluate this method of protection, soft gelatin capsules containing suspensions of penicillin in cottonseed oil and in a mixture of linseed oil and peanut

oil were administered to dogs. A comparison of the data presented in Tables 2 and 6 indicates that the administration of penicillin with oil in single oral doses produced significantly lower concentrations of penicillin in the sera and urine of dogs than those produced by single doses of penicillin with the buffering substances and antacids. However, traces (< 0.2 unit per cc.) of penicillin were detected in the sera for as long as 6 hours.

Summary. The acid inactivation of orally administered penicillin can be reduced appreciably by the simultaneous administration of protective substances. Relatively high concentrations of penicillin can be produced and maintained in the blood and urine of dogs following the oral administration of penicillin with such protective substances as soluble alkaline buffer salts, certain antacids and certain edible proteinic materials. It appears that the use of edible proteinic materials as protective agents for penicillin may permit absorption with no danger of untoward effects.

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STREPTOMYCIN IN THE TREATMENT OF CERTAIN GRAM-NEGATIVE BACILLUS INFECTIONS OF THE CENTRAL NERVOUS SYSTEM

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GRAM-NEGATIVE bacillus infections of the meninges are infrequent when compared with other bacterial meningitides, but they are common enough to be of importance, particularly inasmuch as they are attended by high mortality rates. This report deals with 5 cases of such infections in which recovery followed streptomycin treatment.

The causative organisms were *Pseudomonas aeruginosa* and *Haemophilus influenzae* each in 2 cases and *Bacillus proteus* in 1 case. These are all gram-negative, aerobic, non-sporulating bacilli. *Ps. aeruginosa* (*Bacillus pyocyaneus*) is noted for the bluish green pigment which it produces under certain circumstances. All 3 organisms occur as normal saprophytic inhabitants of the upper respiratory or the gastro-intestinal tracts of man and animals but occasionally produce severe infectious processes. *Ps. aeruginosa* and *B. proteus* are commonly encountered in infections of the genito-urinary tract while *H. influenzae* (the influenza bacillus of Pfeiffer) is most often encountered in meningitis in small children. Each of these organisms may, however, invade any portion of the body and infections due to these bacteria have been reported in the eye,^{33,42,46,74} ear,^{20,50,74} nasal accessory sinuses,^{20,50,74} pharynx,^{42,50,74} larynx,⁴² endocardium,^{28,42} lungs,^{42,50,74} gastro-intestinal tract,^{42,50,74} genito-urinary tract,^{42,50,74} peritoneum,^{42,50,74} liver,^{42,74,77} bones^{50,62,74} and joints,^{42,74} meninges,^{8,42,50,74} skin^{25,42,74} and wounds.^{48,50}

PSEUDOMONAS AERUGINOSA MENINGITIS.

Pathogenesis. Meningitis due to *Ps. aeruginosa* usually follows direct implantation of the organism into the meninges. Occasionally meningitis due to this organism is noted in the course of a septicemia, the portal of entry for the septicemia being the genito-urinary tract or elsewhere.^{26,73} Direct implantation of *Ps. aeruginosa* into the meninges usually follows trauma, as in a skull fracture or a bullet wound or occurs by direct extension from an adjacent suppurative process such as an otitis media, or, it may be introduced by a contaminated spinal anesthesia or lumbar puncture procedure.²⁶ At least 19 cases of *Ps. aeruginosa* meningitis have been reported which were considered to be the result of a contaminated spinal anesthesia or diagnostic lumbar puncture.^{10,11,26,27,43,64,73,78}

Four additional cases have been reported recently following intrathecal penicillin treatment for pneumococcal meningitis. Two of them died. The source of the *B. pyocyaneus* was traced in 2 of the cases to penicillin solutions contaminated by syringes used to withdraw the drug for injection.^{31a}

Treatment and Mortality. Evans²⁶ and Kerman *et al.*⁴³ reviewed the previously reported cases of *Ps. aeruginosa* meningitis and found mortality rates ranging from 52 to 85% in different groups of cases. The higher mortality rates were noted in patients with other complicating conditions or where the pyocyaneus infection involved other parts of the body. In meningitis due

to this organism, without infection elsewhere, the mortality has usually been about 50%.

Since the advent of sulfonamides and penicillin, these agents have been used singly or in combination in the treatment of 21 reported cases of *Ps. aeruginosa* meningitis with 15 deaths.^{2,13,15,17,43,78} Treatment early in the course of the disease resulted in recovery in 4 cases treated by Wise⁷⁸ with sulfanilamide. The results in other sulfonamide treated cases, however, have not been favorable. *In vitro* experiments have shown *Ps. aeruginosa* to be one of the most resistant organisms to the action of penicillin.^{1,37,39} During the treatment of 400 cases of head wounds with sulfadiazine and penicillin in an Army hospital, Botterell and Magner¹³ encountered 11 cases of *Ps. aeruginosa* meningitis; 9 of them died of this infection despite intensive sulfadiazine and intramuscular and intrathecal penicillin therapy. Agulnik² reported a fatal case in a newborn infant following circumcision. His case was treated with sulfadiazine, sulfapyridine and penicillin. Penicillin has proved of little value in treatment of *Ps. aeruginosa* meningitis^{2,13,17} and has been shown to be without value also in the treatment of pyocyanus bacillus infections elsewhere in the body.^{18,19,48}

The *in vitro* resistance of *Ps. aeruginosa* to streptomycin has been found to be of a relatively high degree when compared with an organism like *Pasteurella tularensis*. The latter is inhibited by 0.15 to 0.3 units of streptomycin per ml.³⁶ whereas most strains of *Ps. aeruginosa* require 25 to 100 units of streptomycin per ml.^{14,21,37,44,60} Streptomycin has been shown to protect mice inoculated with lethal doses of *Ps. aeruginosa*.⁴¹

Recently Cairns *et al.*¹⁷ reported 3 cases of pyocyanus meningitis which were treated by sulfonamides, penicillin and intrathecal streptomycin; all 3 patients died. It is noted, however, that treatment was begun late in the course of the disease in 2 of Cairns' cases—approximately 10 days after onset, while the time of institu-

tion of treatment in the third case was not given.

Case Reports. CASE 1. A 14 year old white male, a known epileptic, was admitted to the hospital after a seizure. A diagnostic lumbar puncture revealed normal spinal fluid. Twenty-four hours later the temperature rose, signs of meningitis developed and a second lumbar puncture revealed purulent fluid containing 1300 leukocytes per c.mm. of which 95% were polymorphonuclears. Treatment with intrathecal and intramuscular penicillin and oral sulfadiazine was begun. Repeated lumbar punctures revealed similar cytologic findings and *Ps. aeruginosa* was cultured from each specimen of cerebrospinal fluid.

No improvement followed the use of penicillin and sulfadiazine. On the 4th day penicillin was stopped and streptomycin therapy instituted. The first dose consisted of 0.05 gm. (50,000 units) intrathecally and 1 gm. (1,000,000 units) intramuscularly; this was followed by 1 gm. intramuscularly every 6 hours for a period of 7 days. He was given 2 intrathecal injections of streptomycin, 0.05 gm. each, on the following day, and thereafter 1 daily intrathecal injection of 0.05 gm. for 7 days. Sulfadiazine therapy was stopped on the 9th day of the disease because of the development of crystalluria.

The temperature returned gradually to normal during the first 4 days following institution of streptomycin therapy and clinical improvement was rapid. Daily spinal fluid examinations showed a decrease in the total number of leukocytes with an increase in the percentage of lymphocytes. Cultures of the spinal fluid revealed *Ps. aeruginosa* on the 2nd and 4th days of therapy but later ones were all negative. A total of 28 gm. of streptomycin was given intramuscularly and 0.45 gm. intrathecally. Except for some fever there were no untoward reactions to the streptomycin. The patient was discharged from the hospital 20 days after onset of his disease, apparently cured and with no evidence of residual neurologic damage. The relevant findings in this case are shown in Figure 1.

CASE 2. The more important findings in this case are shown in Figure 2. On the 11th day of this infant's life an ulcerated area on a congenital cervical meningocele was debrided. One day later signs of men-

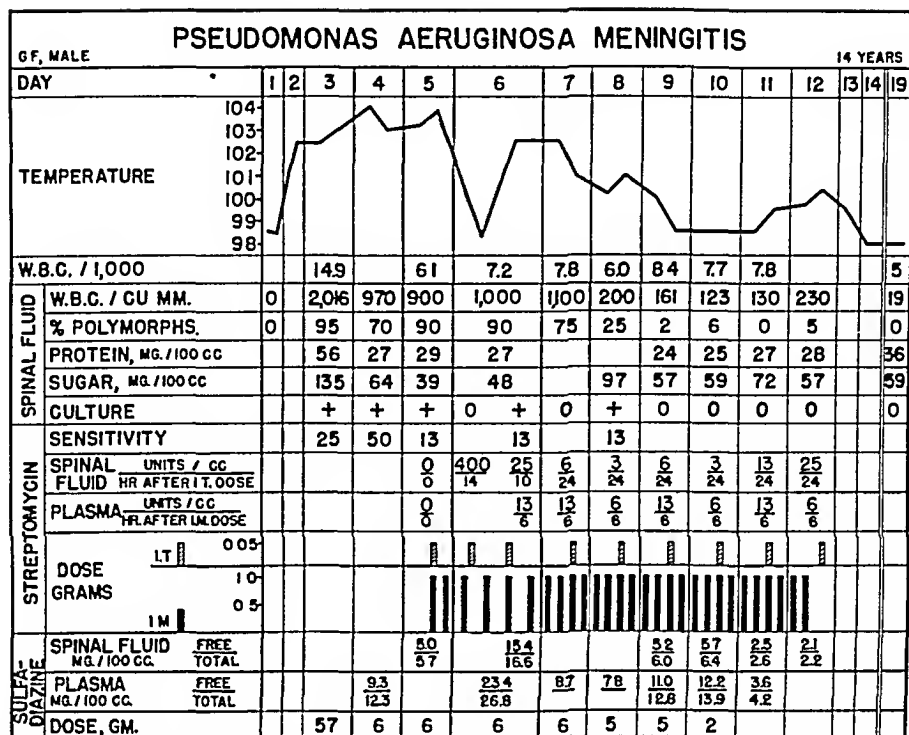
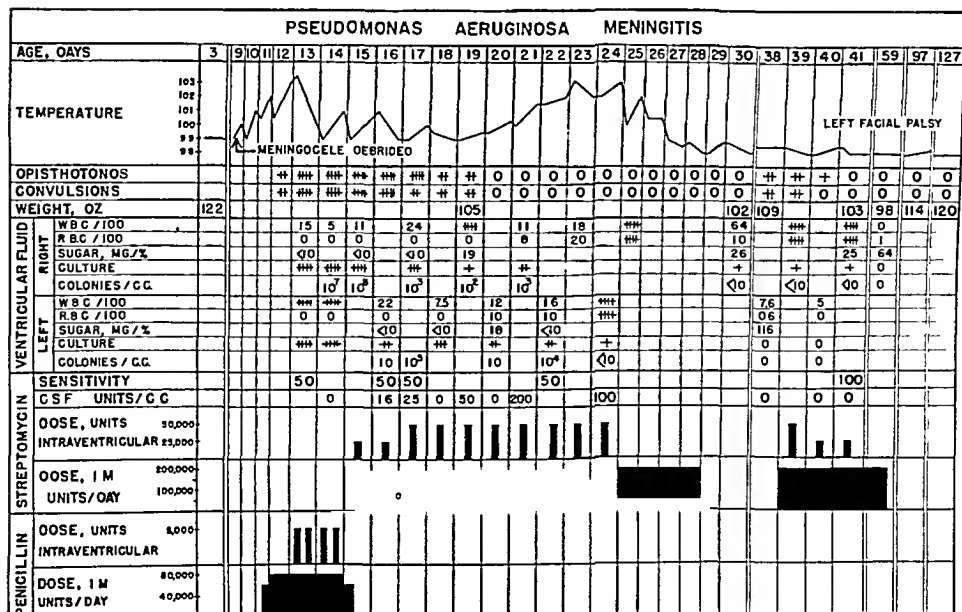


FIG. 1.—Relevant findings in Case 1. Penicillin (not shown in the figure) was given by intermittent intramuscular injections following the first rise in temperature and intraspinally after each of the lumbar punctures done on the 3rd and 4th days but was discontinued when streptomycin was begun.



ingitis developed and *Ps. aeruginosa* was cultured from cerebrospinal fluid obtained by puncture of the ventricle through the fontanelle. After 4 days of ineffective treatment with intramuscular and intraventricular penicillin, that drug was stopped and streptomycin treatment started. The dose of streptomycin was 0.05 gm. every 6 hours intramuscularly and 1 intraventricular dose of 0.025 to 0.05 gm. daily in alternate lateral ventricles. Convulsions and opisthotonos, which were present before this therapy, gradually subsided and the temperature returned to normal within 5 days after institution of streptomycin therapy. From the 6th to the 10th day of streptomycin treatment the temperature showed a gradual rise and at this time intraventricular streptomycin was stopped. During this period the ventricular fluid had become somewhat bloody in appearance. Four days after cessation of the local streptomycin injections the temperature returned to normal and the cerebrospinal fluid had cleared markedly. Cultures of the fluid from the right lateral ventricle were positive for *Ps. aeruginosa* through the 10th day of therapy and from the left lateral ventricle through the 27th day of treatment. A right facial paralysis appeared on that day and persisted. The infant was discharged from the hospital 8 weeks after cessation of therapy, apparently cured of the meningitis but with evidence of residual central nervous system damage. A total of 6.5 gm. streptomycin was given by the intramuscular route and 0.55 gm. by the intraventricular route.

BACILLUS PROTEUS MENINGITIS. *Pathogenesis.* Meningitis due to *B. proteus* usually occurs by direct extension from an adjacent otitis media or mastoiditis.⁵⁰ It has occasionally been reported in the course of septicemia associated with infections in other parts of the body.⁵⁰ No instance of this condition occurring as a result of a spinal anesthesia or lumbar puncture procedure was found in the literature.

Treatment and Mortality. Prior to the advent of sulfonamides the mortality rate of meningitis due to *B. proteus* was over 90%. The use of sulfonamides has apparently been associated with a reduction

in the mortality rate in the few cases that have been reported.^{9,15,22,32,35,51,53,55,70}

B. proteus has been considered resistant to penicillin, 5 to 10 units per ml. being necessary to inhibit this organism.^{1,29,37,40} Stewart,⁶⁷ however, postulated that despite the relatively high degree of resistance to penicillin, this drug may be useful in treating certain *B. proteus* infections where the penicillin can be applied topically in high concentrations. He reported the elimination of *B. proteus* from the ears of certain patients with chronic suppurative otitis media by the use of high local concentrations of penicillin in the form of a gel. On the basis of the relatively high degree of resistance of *B. proteus* to penicillin, however, the use of this drug in the treatment of meningitis due to *B. proteus* would not seem indicated.

B. proteus is moderately sensitive *in vitro* to streptomycin, being inhibited by 2 to 8 units per ml.^{14,21,44,60} Streptomycin also protects chick embryos against experimental infections with *B. proteus*.⁵⁷ Keefer's²¹ report on the clinical use of streptomycin includes 3 cases of *B. proteus* meningitis, 1 due to *B. proteus morgani* and the others due to *B. proteus vulgaris*. One of the patients with *B. proteus vulgaris* died; the other 2 patients survived. The time of institution of treatment in relation to the course of the disease was not stated.

CASE 3. A 4 month old infant developed signs of meningitis following an operation on a congenital meningocele. Culture of the meningocele fluid revealed *B. proteus morgani*. After 6 days of treatment with penicillin given intramuscularly and into the meningocele sac and 2 days of oral sulfadiazine, there was clinical improvement and the fever was decreasing but *B. proteus morgani* was still present in cultures of the meningocele fluid.

At this point other medications were stopped and streptomycin therapy begun. Streptomycin, 0.05 gm., was injected directly into the meningocele sac once daily for 7 days and 0.1 gm. was given intramuscularly every 6 hours for 10 days. Cultures of the meningocele fluid were negative after

streptomycin treatment was begun but the temperature showed a gradual upward swing and the infant seemed worse clinically. Sulfadiazine treatment was reinstituted and the local injections of streptomycin were discontinued on the 7th day of this therapy. Four days later the temperature returned to normal and the infant seemed better clinically. Although clinical improvement coincided with the reinstitution of sulfadiazine it seems that streptomycin was chiefly responsible for the favorable result in view of the fact that cultures of the meningocele fluid became negative only after institution of streptomycin treatment. Subsidence of

the low bactericidal properties of the blood against *H. influenzae*, Type b, in infancy, as shown by Fothergill and Wright.³¹ Pittman⁵³ classified some of the smooth, encapsulated strains of *H. influenzae* into Types a and b, and later described 4 additional types on the basis of a precipitin test.^{58a} Type b is the causative agent in about 95% of the cases of meningitis due to *H. influenzae*.^{4,59,65} Dochez *et al.*²³ noted that during experimental infections of chimpanzees with the virus of the common cold, when *H. influenzae* is present in the

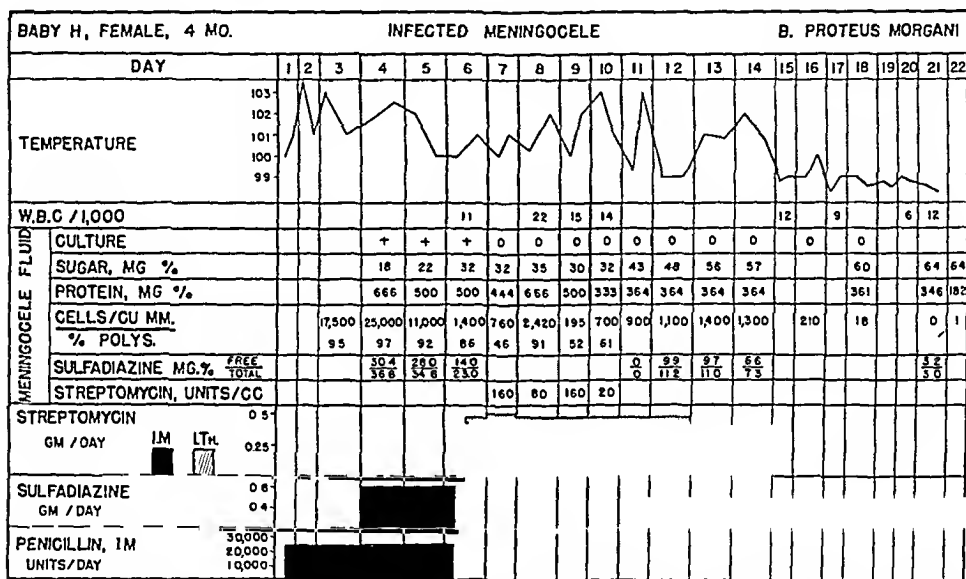


FIG. 3.—Significant data in Case 3. In addition to the therapy shown in this figure penicillin was injected into the meningocele sac daily until streptomycin treatment was started.

fever and clinical improvement also coincided with cessation of injections of streptomycin into the meningocele sac. The infant had an uneventful convalescence. A total of 4.8 gm. of streptomycin was given by the intramuscular route and 0.35 gm. by the intrameningocele route. The more important findings in this case are summarized in Figure 3.

HEMOPHILUS INFLUENZÆ MENINGITIS.
Pathogenesis. *Hemophilus influenzae* meningitis is chiefly a disease of early childhood, 60 to 80% of the cases occurring during the first 2 years of life.⁷¹ This age incidence may be explained, in part, by

nasopharynx of these animals, a transformation takes place from the serologically non-type-specific rough form of *H. influenzae* to the serologically specific smooth form; during healthy periods there is a reversion to the rough form. Smooth pathogenic strains of *H. influenzae* are encountered most often in the human nasopharynx during acute inflammatory processes while rough and presumably non-pathogenic strains are most often found in the normal nasopharynx.^{34,68} Meningitis is probably acquired by invasion of the smooth pathogenic strain through the

respiratory tract by way of the blood stream.

Treatment and Mortality. The mortality of *H. influenzae* meningitis has been reduced from 80 to 98% to 15 to 50%^{3,5,20,61,66,72} since the introduction of combined sulfonamide and type-specific rabbit antiserum therapy. *H. influenzae* has been considered relatively resistant to penicillin.^{1,29,39} Straker⁶⁹ and Forgacs,³⁰ however, reported the isolation of smooth strains, Type b, from human meningeal infections that were sensitive to penicillin to about the same degree as the standard Oxford strain of *Staphylococcus aureus*. Hewitt and Pittman³⁸ tested the sensitivity of 38 strains of *H. influenzae* isolated from cases of human infection and found them to be inhibited by 0.18 to 1.5 units per ml. of commercial penicillin (predominantly penicillin G) and by 0.05 to 0.75 unit per ml. of penicillin X. Forgacs *et al.*³⁰ describe improvement in a patient with *H. influenzae* Type B meningitis on penicillin therapy alone. McIntosh and Drysdale⁴⁹ treated a case of *H. influenzae* Type b meningitis successfully with penicillin and sulfamezathine. The organism isolated from this patient was somewhat less sensitive to penicillin than the standard staphylococcus. Landau⁴⁵ described an infant with an empyema due to *H. influenzae* Type b which persisted despite sulfadiazine, type-specific antiserum and a thoracotomy, and apparently cleared up only after institution of penicillin irrigations of the empyema cavity. The total number of reported cases of *H. influenzae* meningitis that were treated with penicillin are too few to warrant any conclusions concerning its efficacy in this disease.

H. influenzae has been found *in vitro* to be sensitive to streptomycin, being inhibited by 1.56 to 15 units per ml.^{6,21,38,52} Alexander and Leidy⁶ found that streptomycin protects mice against experimental *H. influenzae* infections and that this protection is not enhanced by the concurrent use of sulfadiazine. They also found that the streptomycin alone is more effective against *H. influenzae* infections in mice

than Type b specific antiserum used in conjunction with sulfadiazine. Hewitt and Pittman³⁸ found that streptomycin is the most effective agent in protecting mice against experimental infections with *H. influenzae*.

Clinical in Contrast to Experimental Reports. Logan and Herrell⁴⁷ reported the use of streptomycin along with sulfonamides and specific antiserum in the treatment of 4 patients with *H. influenzae* meningitis. The infection was apparently controlled in each of these 4 patients but 1 of them later died of hydrocephalus. Butler *et al.*¹⁶ reported recovery of a patient with *H. influenzae* meningitis treated with streptomycin, sulfadiazine and Type b rabbit antiserum.

Birmingham *et al.*¹² reported on the treatment of 8 cases of *H. influenzae* meningitis—4 patients recovered, 3 died and in 1 streptomycin therapy was given up in favor of sulfadiazine and antiserum. In 1 of the patients who died, the organism became resistant to streptomycin during treatment. Nussbaum *et al.*⁵⁶ used streptomycin and sulfadiazine in the successful treatment of 3 infants below the age of 2 years. Weinstein⁷⁵ used streptomycin in 9 cases of *H. influenzae* meningitis with 2 deaths, 1 of them due to a complicating staphylococcal infection. The prompt clinical and bacteriologic response to streptomycin therapy in the survivors was dramatic. In the 100 cases of *H. influenzae* meningitis treated with streptomycin under the auspices of the National Research Council,²¹ the mortality was 17%. In many of these patients, streptomycin treatment was begun only after other forms of treatment had failed. Alexander *et al.*⁷ more recently reported 25 cases treated with streptomycin alone or combined with other agents, with 3 deaths. In 2 of her cases resistant strains of *H. influenzae* developed during streptomycin therapy.

CASE 4. An 8 month old infant was admitted to the hospital after 1 day of fever, hyperirritability and emesis and was found

to have *H. influenzae* Type b meningitis. Without other previous or concomitant therapy, streptomycin treatment was instituted 36 hours after the onset of symptoms. The streptomycin was given intrathecally, 0.05 gm. as an initial dose and then 0.025 gm. was given once a day for 8 days. In addition, 0.2 gm. was given intramuscularly every 6 hours for 16 days. Cultures of the cerebrospinal fluid promptly became negative and the cerebrospinal fluid sugar level returned to normal within 2 days after this treatment was started. The temperature showed a decided drop on the 4th day of treatment and this was associated with clinical improvement. There were irregular

temperature rose abruptly and the signs of meningitis became more marked. On that day the cerebrospinal fluid showed an increase in the number of cells and gram-negative bacilli were noted in stained smears of the cerebrospinal fluid but cultures of the same fluid were negative. Other medications were then stopped and streptomycin was begun on the 12th day of the disease. The streptomycin was given intramuscularly, 0.2 gm. every 6 hours for 6 days, and intrathecally 0.025 gm. once daily on 3 consecutive days. During the period of streptomycin therapy the fever persisted. Signs of serum sickness were noted on the 14th day of the disease. The number of cells in the

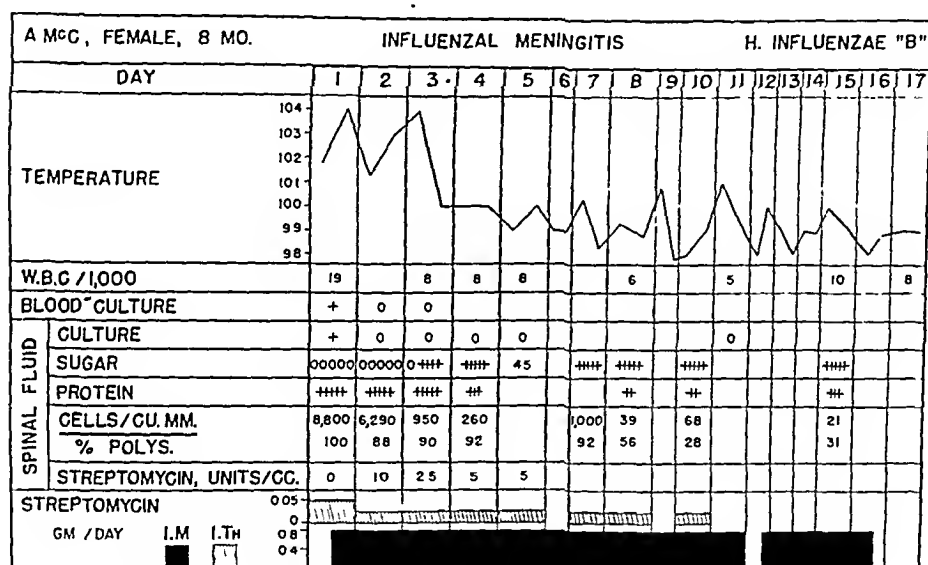


Fig. 4.—Case 4. Streptomycin was the only antibacterial agent used in this case.

elevations of temperature through the 15th day of treatment. A total of 11.6 gm. of streptomycin was given intramuscularly and 0.225 gm. intrathecally. The infant was apparently cured, without evidence of residual central nervous system damage. Figure 4 shows the relevant findings in this case.

CASE 5. An 11 month old infant was admitted to the hospital after a few hours of illness and found to have meningitis. Cultures of the blood and cerebrospinal fluid yielded *H. influenzae*, Type b. For a period of 10 days treatment consisted of sulfadiazine, penicillin and 2 injections of specific rabbit antiserum. During this time the patient's condition seemed to improve slightly. On the 11th day, however, the

spinal fluid decreased and organisms could no longer be seen in stained smears after the 1st day of streptomycin therapy. The temperature, however, did not return to normal until several days after cessation of streptomycin treatment. A total of 4.4 gm. was given by the intramuscular route and 0.75 gm. intrathecally.

SENSITIVITY OF ORGANISMS. The streptomycin sensitivity of the organisms obtained from the present cases was determined by the serial dilution tube method.^{27a} The *Ps. aeruginosa* isolated from Case 1, before streptomycin treatment, grew in 250 units per ml. penicillin but was completely inhibited by 25 to

50 units per ml. streptomycin on different occasions. The *Ps. aeruginosa* obtained from Case 2 before streptomycin therapy was completely inhibited by 50 units per ml. streptomycin. Strains of *Ps. aeruginosa* cultured from Cases 1 and 2 during the streptomycin treatment were no more resistant to streptomycin than the pretreatment strains. The *B. proteus morganii* isolated from Case 3 before treatment was completely inhibited by 50 units per ml. streptomycin. The *H. influenzae* from Case 4 was completely inhibited by 1.56 units per ml. streptomycin. Sensitivity of the *H. influenzae* from Case 5 was not determined since the organism seen in smear before treatment could not be grown and the earlier cultures from this patient were not available.

STREPTOMYCIN CONCENTRATIONS IN THE CEREBROSPINAL FLUID AND BLOOD. Streptomycin concentrations in cerebrospinal fluid and plasma were determined by a serial dilution tube method using strain "T" of *Klebsiella pneumoniae* as the test organism.^{27a} Streptomycin, usually 0.05 gm. (50,000 units), was given topically once daily to these patients. In Case 1, a 14 year old boy, the concentration of streptomycin in the cerebrospinal fluid 24 hours after the previous intrathecal injection of 50,000 units ranged from 3 to 25 units per ml., during the period of treatment. In this same patient, cerebrospinal fluid contained 400 units per ml. streptomycin 14 hours after the local injection of the same amount. In Case 2, a 2 week old infant, streptomycin concentrations in the ventricular fluid obtained 24 hours after a previous intraventricular injection of 50,000 units ranged from 0 to 200 units per ml., over a period of several days. The meningeal fluid in Case 3, a 4 month old infant, obtained 24 hours after a previous intrameningeal injection of 50,000 units contained from 20 to 160 units per ml. In Case 4, an 8 month old infant, cerebrospinal fluid concentrations of streptomycin ranged from 2.5 to 10 units per ml., 24 hours after the previous intrathecal injections of 50,000 units of streptomycin.

Plasma streptomycin concentrations in Case 1, obtained 6 hours after intramuscular injections of 1 gm. (1,000,000 units) of streptomycin, ranged from 6 to 13 units per ml., during the treatment period.

UNTOWARD EFFECTS OF STREPTOMYCIN. The intramuscular administration of streptomycin was attended by no harmful effects save for the development of a subcutaneous sterile abscess at the site of repeated intramuscular injections in Case 2. The total daily intramuscular dose of streptomycin ranged from 0.2 gm. for Case 2, the newborn infant, to 4 gm. for Case 1, the 14 year old boy. The individual intramuscular doses were given every 6 hours in 1 to 4 ml. of sterile normal saline.

In Cases 1, 2 and 3, there was an elevation of temperature and an increase in cells in the cerebrospinal fluid associated with the injections of topical streptomycin. Birmingham *et al.*¹² noted an aggravation of the meningeal signs and an increase in the number of cells in the cerebrospinal fluid in 2 patients receiving intraspinal streptomycin. The increases in fever, in the number of cells in the cerebrospinal fluid and in the severity of clinical signs in Cases 2 and 3 seem definitely related to the local injections of streptomycin, since they occurred during treatment and subsided promptly after the local injections were stopped. In Case 1, there was an increase in the number of cells in the cerebrospinal fluid associated with fever on the 6th day of intrathecal therapy; the fever promptly subsided after cessation of the intrathecal streptomycin, but this also coincided with the cessation of intramuscular streptomycin.

The local injections of streptomycin were usually given daily and consisted of 0.05 gm. in 1 ml. of sterile normal saline. Cerebrospinal fluid was withdrawn into the syringe containing the streptomycin solution and the dose slowly delivered. No immediate untoward effects from these injections were observed.

Comment. In evaluating the rôle of streptomycin in the cases of *Ps. aeruginosa*

meningitis, in Case 1, the clinical and bacteriologic response of the patient following institution of therapy was prompt. In this patient, the infection followed lumbar puncture and streptomycin was started relatively early in the course of the disease but only after several days of apparently ineffective penicillin and sulfadiazine therapy. In Case 2, streptomycin therapy was not begun until the 7th day of the disease after 4 days of ineffective penicillin therapy; the response of the infant to streptomycin was only gradual and there was evidence of residual damage to the central nervous system after treatment. However, the fact that the infant survived at all is remarkable inasmuch a *Ps. æruginosa* is apparently a much more virulent organism for infants than for adults. In the period of 7 days before streptomycin was begun, there was more than ample time for *Ps. æruginosa* to have inflicted severe damage on the central nervous system such as has been reported by Cairns *et al.*¹⁷ Evidently streptomycin was responsible for the survival of this infant.

In Case 3, with *B. proteus morgani* meningitis, organisms disappeared from the cerebrospinal fluid only after the institution of streptomycin therapy, though some clinical improvement had occurred during the preceding period while penicillin and sulfadiazine were being given. Here again the recovery may be ascribed to the streptomycin.

Case 1 was from the Fifth Medical Service (Boston University), Cases 2 and 3 were from the Neurosurgical Service and Cases 4 and 5 were from the Pediatrics Service. We are indebted to the physicians and surgeons of these services for the privilege of studying these cases.

The streptomycin was provided by the National Research Council from supplies assigned for clinical investigations recommended by the Committee on Chemotherapeutics and Other Agents.

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In Case 4, with *H. influenzae* meningitis, streptomycin therapy was attended by a prompt clinical and bacteriologic response. Since no other medications were used in this patient, streptomycin would seem responsible for the cure obtained in this infant. The rôle of streptomycin in Case 5, however, is more difficult to evaluate. In view of the failure of the patient to show an adequate response to the previous treatment, this infant, in addition to having serum sickness, probably was undergoing an exacerbation of her disease. Such a course is not uncommon in *H. influenzae* meningitis.⁷² The severity of the meningeal and cerebral symptoms, the increase in the number of cells and the occurrence of organisms in the cerebrospinal fluid all suggest that the institution of streptomycin at this point may have affected a resolution of the disease process.

The transient untoward effects of local use of streptomycin in Cases 2 and 3 and probably in Case 1, would indicate that the intraventricular and intrathecal routes, for the administration of streptomycin should be used with caution.

Conclusion. Two cases of *Ps. æruginosa* meningitis, 1 case of *B. proteus morgani* meningitis and 2 cases of *H. influenzae* Type b meningitis were successfully treated with streptomycin. Streptomycin, administered by the intrathecal and intramuscular routes would seem to be the drug of choice in the treatment of meningitis due to these gram-negative bacilli.

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THE SIGNIFICANCE OF THE MYELOID MATURATION CURVE IN MATERIAL ASPIRATED FROM THE STERNAL BONE MARROW

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THE differential count of material aspirated from the sternal marrow cavity offers a method for the study and evaluation of cytologic changes which occur in diseases involving the hematopoietic system. The data upon which this study was based consist of a series of differential cell counts of the bone marrow from 165 individuals, 159 of whom were afflicted, either primarily or secondarily, with a variety of diseases affecting the hemo-lympho-poietic system. The bone marrow aspiration technique justifies itself by making available data upon which a more specific diagnosis may be made and by providing a method for further inquiry into the causes and nature of disorders affecting the formation of blood cells.

Methods. I. THE TECHNIQUE OF STERNAL PUNCTURE AND THE PREPARATION OF BONE MARROW FOR EXAMINATION. All samples of bone marrow were obtained by puncture of the sternal marrow cavity in the midline at the level of the third rib. Less than 0.5 cc. of marrow pulp was forcibly aspirated. Coverslip preparations were made, stained with Wright's stain, and differential counts of 300 to 500 marrow cells were made from many suitable fields.

II. CRITERIA OF CELL TYPES. (a) *The Myeloid Series.* The classification by which the cells of this series were identified is that described by Naegeli,⁹ and further defined by Nordenson,¹⁰ and Wintrobe.²²

(b) *The Erythroid Series.* The descriptions of the cells of this series also follow those given by Naegeli⁹ and the differential criteria of classification are consistent with those described by Segerdahl,¹⁹ Nordenson,¹⁰ Schulten,¹⁷ and Wintrobe,²² with the excep-

tion that Schulten refers to the megaloblast of Naegeli as a pro-erythroblast. In this paper, the erythropoietic cells were differentiated into the *megaloblast*, the earliest definable form of the erythroid series, the *erythroblast*, the intermediate form containing a "spoke wheel" nucleus, and the *normoblast*, the smallest form containing a dense pyknotic nucleus and hemoglobinized cytoplasm.

(c) *The Lymphocytic, Monocytic and Plasma Cell series* were classified according to the criteria of Naegeli.

III. ANALYSIS OF DATA. All numerical data were analyzed by the use of standard statistical methods.²

The normal series of bone marrow differential counts consists of 1 analysis from each of 6 normal individuals. The *means* and *standard deviations* for each cell type are shown in Table 1. Those figures which are significant in terms of their *standard errors* are *italicized* and are used as a basis for judging the unusual occurrence of any given type of cell found in the bone marrow in conditions of disease. Variations of more than 3 *sampling errors* from the *mean* of the normal group are considered to have probable diagnostic significance, and variations of 2 to 3 sampling errors are considered to have only possible diagnostic significance.

A selection of authors whose techniques agree with and whose data resemble those presented here is given in Table 2. For purposes of comparison the differential counts of the myeloid series were expanded to a base of 100.

The clinical series of bone marrow differential counts were tabulated on 159 patients suffering from a variety of diseases which for reasons of simplification were classified into 24 categories. The calculated *mean* for each cell type for each disease is listed in Table 3.

Those values which are significant in terms of their *standard errors* and which deviate more than 3 *sampling errors* from the *mean* of the normal group are *italicized* and those which deviate between 2 and 3 *sampling errors* are indicated with **bold type**. The *italics* in parenthesis indicates sig-

their occurrence in the normal bone marrow, the unusual exception being the value of 15.9 for unclassified cells (primitive histiocytes) which occurs in monocytic leukemia.

BRIEF REVIEW OF THE LITERATURE.
According to the literature, the differential

TABLE 1.—MEAN VALUES OF THE DIFFERENTIAL CELL COUNTS OF THE BONE MARROW FROM 6 NORMAL INDIVIDUALS

		Mean	±	Standard error of the mean	Standard deviation (σ)	±	Standard error of the σ
Myeloblasts		1 0	±	0 4	0 9	±	0 3
Promyelocytes		4 0	±	0 6	1 4	±	0 4
Myelocytes	N	10 2	±	1 3	3 1	±	0 9
	E	0 8	±	0 2	0 5	±	0 1
	B						
Metamyelocytes	N	13 2	±	1 1	2 7	±	0 8
	E	1 3	±	0 2	0 4	±	0 1
	B						
Polymorphonuclear leukocytes	N { NF	24 6	±	3 9	9.7	±	2 8
	F	10.0	±	1 5	6.2	±	1 8
	E	0.3	±	0 1	0 3	±	0 1
	B						
Total granulocytic series					65.4		
Lymphoblast							
Early lymphocyte							
Lymphocyte		10 3	±	1 7	4 4	±	1 2
Plasma cell		1 5	±	0 5	1 3	±	0 4
Total lymphocytic series					11.8		
Monoblast		0 2	±				
Promonocyte		0 2	±				
Monocyte		0 5	±				
Total monocytic series					0.9		
Megaloblast		0 6	±	0 8	1 4	±	0 6
Erythroblast		8 0	±	2 5	6 2	±	1 8
Normoblast		12 0	±	2 6	6 5	±	1 9
Total erythrocytic series					20.6		

Values which are significant in terms of their standard errors are italicized.

TABLE 2.—A COMPARISON OF DATA FROM SELECTED AUTHORS SHOWING THE MATURATION CURVE OF THE MYELOID SERIES OF NORMAL BONE MARROW OBTAINED BY ASPIRATION
(VALUES EXPANDED TO A BASE OF 100)

	No. cases	Myeloblasts	Promyelocytes	Myelocytes	Metamyelocytes	PMN NF	PMN F
Segerdahl ¹⁰	52	1 9	2 1	24 2	23 2	15 5	33 1
Isaacs ³	11	3 4	..	5 4	40 7	25 3	25 3
Scott ¹⁴	6	2 6	6 5	22 0	22 5	23 0	23 5
Plum ¹³	40	2 5	4 2	13 8	13 9	50 3	15 3
Wintrobe ²²	..	3 1	7.8	21 2	33 8	34 2	
Osgood ¹²	..	1 9	2 2	22 2	23 0		37 4
Lucia and Hunt	6	2.0	6 1	16 7	22 1	37 4	15.7

nificant deviations from the normal but the *standard errors* of these values are so great, possibly due to the smallness of the sample under consideration, that they are of less significant value for comparative purposes. The values which are in **bold italics** are of diagnostic significance because of their magnitude and because of the scarcity of

count of the bone marrow has been regarded as of definite value in:

1. *The Differential Diagnosis of the Anemias*. Reich¹⁵ described several cases in which he was able to differentiate the variety of anemia by means of the differential count of the bone marrow. Isaacs³

TABLE 3.—THE CALCULATED MEAN VALUES OF THE CELL TYPES IN BONE MARROW OBTAINED BY ASPIRATION FROM NORMAL AND DISEASED INDIVIDUALS

	No. cases	Myelo- blasts	Promyelo- cytes	Myelocytes			Metamyelocytes			Polymorphonuclear cells					Lymphocytic series												
				N	E	B	N	E	B	NF	F	E	B	Lymphoblasts	Polylymphocytes	Lymphocyte	Plasma cells	Monoblast	Promonocyte	Monocyte	Megakloblast	Erythroblast	Normoblast	Primitive cells	Unclassified cells	Giant cells	
1. Normal	6	1.6	4.0	16.2	0.8	..	13.2	1.3	..	24.6	10.0	0.3	16.3	1.5	0.2	0.2	0.5	0.8	8.6	12.0	0.9	0.3	
2. Leukemia: Lymphatic	8	0.8	3.6	7.6	1.2	..	6.3	0.8	0.1	7.5	2.8	0.4	0.1	0.3	12.8	3.3	0.3	0.3	3.4	9.8	1.4	0.2	
3. " Myeloid	7	(4.0)	(14.6)	17.7	1.2	..	12.8	1.5	..	21.7	6.6	0.8	1.2	2.1	0.5	0.6	..	0.3	0.6	3.3	6.5	3.2	0.8
4. " Monocytic	3	..	3.6	3.4	4.3	0.3	2.6	1.2	..	4.7	1.5	0.7	0.3	6.5	3.4	5.8	14.1	23.1	4.1	2.1	15.9	0.2
5. Lymphosarcoma	2	0.5	1.1	5.3	0.2	..	7.3	0.4	..	6.3	1.2	0.3	3.2	5.7	2.4	0.2	1.9	13.0	0.7
6. Plasma cell myeloma	7	1.4	2.6	11.8	0.6	..	7.3	1.3	..	9.5	4.0	1.3	4.4	16.9	13.6	0.7	0.8	6.3	13.3	1.8	3.1	..	1.3
7. Leukemoid reaction	4	1.1	4.6*	10.6	1.2	..	11.4	2.1	..	18.0	11.0	8.9	4.5	14.6	1.3	0.3	0.9	2.5	10.1	0.6	1.3	..	0.7
8. Anemia: Pernicious	7	1.6	4.8	14.7	1.7	..	13.5	0.6	..	14.4	7.2	0.6	0.2	7.4	0.7	0.2	5.7	9.6	14.2	1.8	0.7	..	0.2
9. " Secondary	15	1.2	3.3	11.2	1.8	..	12.7	0.6	..	14.8	3.9	0.5	0.2	7.4	2.3	0.1	..	0.3	0.8	7.4	20.4	1.3	0.2	0.1
10. " Hemorrhagic	5	1.6	5.5	16.8	1.8	..	17.3	1.3	..	14.9	6.0	0.3	0.4	0.1	8.5	6.7	0.6	1.7	0.4	13.5	1.5	0.3	0.4
11. " Hemolytic	3	0.6	1.4	7.1	1.0	..	11.8	0.8	..	13.1	4.1	9.6	2.0	0.1	1.7	16.6	24.5	2.1	0.2
12. " Myelocytotic	4	1.0	4.0	10.4	2.0	0.1	13.2	2.4	0.7	25.6	8.1	0.5	0.3	0.3	6.6	0.9	..	1.2	1.1	1.1	5.0	12.3	3.1	..	0.2
13. " Cause unknown	15	1.3	3.6	11.8	1.7	6.1	11.6	1.1	..	16.1	4.9	0.6	0.2	0.1	9.5	1.2	0.2	2.4	16.4	26.2	1.5	..	0.2
14. " Miscellaneous	8	1.4	3.8	12.1	0.8	..	14.2	1.0	..	17.3	7.0	0.5	11.8	1.0	0.2	0.4	0.7	5.0	16.8	0.8	0.8	..
15. Hodgkin's disease	12	1.5	6.0	12.3	1.9	..	17.0	1.2	..	21.9	6.4	0.8	0.1	0.1	8.7	1.6	0.2	..	0.2	0.3	5.2	12.8	1.4	0.1	..
16. Polycthemia	3	1.4	2.6	8.4	1.1	..	11.9	1.2	..	18.3	18.1	0.2	0.5	7.0	1.6	1.7	0.2	7.4	17.6	1.9	..	0.1
17. Thrombocytic purpura	5	1.9	5.6	16.8	0.8	..	12.7	0.5	..	16.7	0.0	0.4	0.2	13.1	6.8	0.7	0.2	8.2	17.4	1.4
18. Cong. hemolytic icterus	4	1.3	3.1	8.2	6.6	0.1	9.1	1.4	..	11.4	7.6	0.1	6.0	0.4	0.6	1.6	16.4	30.2	0.9
19. Splenomegaly	16	1.5	5.4	11.4	2.1	..	11.9	1.2	..	17.7	7.3	0.7	0.1	8.3	0.9	0.9	0.3	7.4	26.2	6.8	1.0	0.1
20. Banti syndrome	3	(3.0)	2.8	6.3	1.8	..	13.1	1.4	..	11.3	4.8	0.1	0.1	16.4	0.8	0.8	2.3	13.1	23.0	1.8
21. Boeck's sarcoid	4	1.6	4.5	13.6	2.9	..	13.1	0.5	..	22.2	11.6	0.9	0.1	4.8	0.8	0.3	2.1	8.1	9.7	1.2	2.4	..
22. Lupus erythematosus	2	2.3	(19.8)	14.1	0.5	..	18.7	0.3	..	19.5	7.1	1.0	8.3	2.6	6.3	1.5	16.4	1.6
23. Dorsolateral sclerosis	4	1.5	..	8.6	2.0	..	12.3	1.0	0.1	26.1	11.3	0.5	0.4	7.8	0.8	0.7	0.8	5.3	14.3	1.5	0.5	..
24. Cirrhosis of liver	3	0.8	7.1	13.6	6.3	..	18.1	0.3	..	23.2	10.0	0.9	0.7	6.5	0.9	0.7	0.5	5.6	8.6	1.6
25. Other diseases	15	1.6	5.3	12.0	1.0	..	16.5	1.1	0.1	20.3	8.4	0.6	0.1	6.2	1.2	0.1	..	0.3	0.1	7.0	16.1	1.1	..	0.1

* Includes promyelocyte eosinophil 0.1.

observed a phenomenon in the bone marrow which he designated the stage of "block of growth." He suggested that the anemias may be classified in terms of the stage at which inhibition of the precursors of the red blood corpuscles occurs. For example, inhibition of development at the level of the primitive blast stage would be considered characteristic of aplastic anemia; inhibition of development at the megaloblast stage would be considered characteristic of pernicious anemia, many of the macrocytic anemias, and in some instances of cirrhosis of the liver; and inhibition or delay of development at the level of the normoblast stage would be observed frequently in leukemias and infections.

Our observations, on the other hand, indicate that the only outstanding diagnostic feature of the bone marrow with reference to the erythropoietic series is the presence of a predominance of megaloblasts in pernicious anemia.

2. *Establishing a Diagnosis of a Disorder of the Hematopoietic System.* The differential count of the bone marrow is believed to have diagnostic significance in subleukemic monocytic leukemia and in aplastic anemia;²³ aleukemic lymphatic leukemia;¹⁵ aleukemic leukosis;¹ Gaucher's disease, certain carcinomas, and malaria;²¹ anemias due to deficiency of liver complex, myelomatosis, and subleukemic and leukopenic leukosis;¹⁸ in doubtful or obscure anemias;^{1,4,23} and in doubtful or obscure leukemias.^{1,4,15,18,21,23}

3. *Confirming a Diagnosis of a Disorder of the Hematopoietic System.* This has been demonstrated in multiple myeloma, aleukemic leukemia, and Banti's disease;²³ agranulocytosis, aplastic anemia, polycythemia, hemolytic jaundice, sprue, pernicious anemia, leukopenic infectious monocytosis, and leukemia;²¹ and in kala azar and relapsing fever.¹⁸

Discussion. 1. *The Normal Bone Marrow Differential Count.* A comparison of the mean normal values of the bone marrow differential count found in the publications of a large group of authors, as

well as a selected group (Table 2) chosen because of similarities in techniques, showed such disparity that it was considered inadvisable to refer for interpretation any potentially pathologic bone marrow counts to the "normal" values already published. In other words, the interpretation of a bone marrow differential count must be referred to a set of standard mean values determined by a given observer on a series of normal individuals. Under the best of circumstances when a small amount of marrow pulp is forcibly aspirated and then examined, the differential count will give a quantitative approximation of the qualitative cytologic variation of the marrow *in situ*. An attempt to compare, and use as a base line, the curves of myeloid maturation calculated from the data of various investigators serves no useful purpose because they are not comparable. The differences in actual numbers for the various cell types, as found in the literature, may be due to: (1) differences in nomenclature and definition of cell types; (2) the degree of dilution of the marrow pulp with blood; (3) nutritional and environmental changes to which the population under analysis is subjected; (4) statistical errors induced by small sampling; and (5) variations of chance.

II. THE BONE MARROW DIFFERENTIAL COUNT IN DISEASE. (a) *Pernicious Anemia.* In pernicious anemia there is a marked absolute increase in megaloblasts during relapse and a rapid conversion of megaloblastic to normoblastic marrow after specific treatment.^{1,3,7,10,21} The shift in the curve of maturation in pernicious anemia, from megaloblastic to normoblastic following treatment with liver substance is described by Limarzi and Levinson,⁷ who noted an unusual morphologic cell change involving multipolar mitosis and the formation of multinucleated erythroblasts. According to Nordenon,¹⁰ the disturbance in the maturation process also involves the myeloid series. The promyelocytes and myelocytes become larger than usual and their nuclei become swollen and porous (dyspoietic). The chromatin

framework is condensed and knotted instead of being evenly distributed throughout the nucleus. "The degenerative changes are almost pathognostic for pernicious anemia, though a suggestion of similar changes has been observed in lymphogranulomatosis, granulocytopenias and severe anemias in cancer." Schleicher¹⁶ considered the morphologically altered reticulum found in pernicious anemia to be of diagnostic significance for that disease and its biologic variations. He also stated that, "Under specific therapy or spontaneous remission the diseased reticulum seems to become depleted and thus proliferation of pathologic stem cells ceases. The maturation process of the promegaloblast is apparently promoted, however, developing into a normoblast-like erythroblast rather than [a] true normoblast."

Our data on 7 cases of pernicious anemia show a significant* increase in megaloblasts with evidence of myeloid irritation and a slight shift of the myeloid curve to the left (Table 3).

(b) *Plasma Cell Myeloma*. Vogel *et al.*²¹ noted in plasma cell myeloma a definite increase in plasma cells "ranging from a true plasma type to a more undifferentiated one" and described a case in which 20% of the bone marrow cells were of these varieties.

Our 7 cases of plasma cell myeloma showed a mean incidence of 13.6% plasma cells. This value is statistically significant. An incidence of plasma cell values beyond 6% in the bone marrow may be considered diagnostic of myelomata.

(c) *The Leukemias*. (1) In *myeloid leukemia* the myeloblasts are present in appreciable numbers in the acute form and myelocytes predominate as the disease progresses to the chronic form.^{1,10,20} In our series the myeloid maturation curve shifts to the left in the direction of greater numbers of the earlier forms of the myeloid series (Table 3), the greatest change

being found in the promyelocytes followed by the myelocytes and lastly the myeloblasts. The calculated values for myeloblasts and promyelocytes show a definite deviation from the normal but their significance is diminished because of the smallness of the sample. Similar changes in each cell type may be found in conditions other than myeloid leukemia and therefore these values are not absolutely diagnostic of leukemia but only confirm the clinical impression of leukemia.

(2) In *lymphatic leukemia*, Nordenson¹⁰ differentiates the acute form from the chronic form by the appearance of increased numbers of lymphoblasts in the former and of lymphocytes in the latter. According to Vogel *et al.*²⁰ the bone marrow differential in this condition shows a definite increase in lymphocytes, the precise morphologic characteristics of which were not easily definable.

In *lymphosarcoma*, Dameshek¹ observed the presence of many lymphoblasts, while Vogel *et al.*²¹ found the bone marrow differential to be normal.

Our data show a significant increase in lymphocytes in both lymphatic leukemia and lymphosarcoma. Early forms of the lymphocyte appear to be definitely increased in lymphatic leukemia, but our series of cases is too small to determine the statistical value of this increase. A large number of lymphocytes occurring in the bone marrow may be considered indicative of lymphosarcomatous metastases.

(3) In *monocytic leukemia*, Dameshek¹ reported a marked increase in both monocytes and histiocytes. Vogel *et al.*²⁰ reported 1 case of monocytic leukemia in which there were 45% "monocytic myeloblasts," and 22% monocytes.

Differentiated monocytes appear so infrequently in the normal bone marrow that any definite increase probably has diagnostic significance. Monocytic leukemia is characterized by a marked hyperplasia of primitive reticulum cells. In our

* Significance in this instance is based on comparing the mean of the megaloblasts in the disease group (pernicious anemia) with the mean of the megaloblasts for all groups (1 ± 0.1), since the mean for megaloblasts in the normal group (0.6 ± 0.8) was not a significant figure in terms of its standard error as shown in Table 1.

small series of 3 cases not only were the differentiated monocytes present in large numbers, but the promonocytes, monoblasts and primitive unclassified cells (histiocytes) also appeared in appreciable numbers.

(d) In *secondary anemias*, Nordenson¹⁰ found in bone marrow that myeloid stimulation predominated and that it was accompanied by normoblastic erythropoiesis. Dameshek¹ reported marked erythroblastic responses in hemolytic anemia. In the anemia secondary to nutritional disturbances, Vogel *et al.*²¹ observed normal leukopoietic responses associated with moderate degrees of erythropoiesis.

Our group of 15 cases of secondary anemia includes anemias due to chronic arsenic poisoning, idiopathic hypochromemia with achlorhydria, nutritional disturbances, dysthyroidism, subacute bacterial endocarditis, carcinomatous metastases and senility. In general, there is a definite increase in normoblasts in any condition where there is active regeneration of red blood corpuscles. These findings also occur in the hemolytic and hemorrhagic anemias and are especially noted in the anemia of congenital hemolytic icterus. A general reduction in the cellularity of the marrow is found in aplastic, myelosclerotic and myelophthisic anemias.

(e) In *polycythemia*, the reports of bone marrow counts vary from those showing a generalized proliferation of the megakaryocytes, erythroblasts and myeloblasts (Dameshek¹), to those showing changes characteristic of an excess of maturation factor (Vogel *et al.*²¹). Our observations, as do those of Nordenson,¹⁰ fail to reveal any characteristic findings.

(f) *The marrow in other diseases* not classified as disorders of the hematopoietic system. Vogel *et al.*²¹ classified such diseases according to the findings in the bone marrow as (1) those producing a myelopoietic shift to the right, (2) those producing a myelopoietic shift to the left, and (3) conditions in which the myeloid maturation curve remains normal. Some diag-

nostic entities are found to occur in more than 1 category, indicating that the presence or absence of a shift in the myeloid maturation curve in these disorders is of little or no significance. In these conditions, the shift in maturation which occurs in the bone marrow is a characteristic of the reactivity of the patient to a given disease rather than a characteristic of the disease itself. Therefore, positive alterations in the bone marrow differential counts may be of value only in corroborating a clinical diagnosis.

The differential count of material aspirated from the sternal bone marrow in this group of diseases reveals no findings of diagnostic significance except for those conditions discussed below.

Lupus Erythematosus. Dameshek¹ described 1 case of acute lupus erythematosus in which the bone marrow was hyperplastic and there were small areas of necrosis "affecting particularly the leukopoietic elements. There was an increase in reticulum cells. . . ."

Our data on 2 cases of lupus erythematosus showed bone marrow differential counts characteristic of the "leukemoid" reaction with a definite shift to the left of the myeloid series especially affecting the promyelocytes.

Sarcoidosis. Dressler⁸ was able to diagnose sarcoidosis on the basis of the cellular characteristics of material obtained by bone marrow puncture. We have been unable to confirm these findings in our study of 4 cases.

The Banti Syndrome. According to Limarzi *et al.*,⁶ the earliest stage of the Banti syndrome is characterized by myeloid hyperplasia; later there is maturation arrest of the myeloid and megakaryocytic tissue, and in the final stages, identified by cirrhosis of the liver, the bone marrow shows marked immaturity in erythropoiesis as well as the above cited changes in myelopoiesis. In our study of the Banti syndrome, the bone marrow revealed no significant deviations from the normal.

III. THE SIGNIFICANCE OF EOSINOPHILS

OCCURRING IN THE BONE MARROW. Vogel *et al.*²¹ reported bone marrow differential counts on 15 cases of splenomegaly to be essentially normal with an increase in eosinophilic myelocytes in a few cases. In Hodgkin's disease he found a slight myeloid shift to the left and in some cases an increase in eosinophils and reticulum cells.

Our data showed an increase of eosinophils in Hodgkin's disease, splenomegaly, dorso-lateral sclerosis and in sarcoidosis; all of them chronic diseases characterized by sclerotic or fibrotic changes in the bone-marrow or hematopoietic tissues. Eosinophils appear in relatively increased numbers in allergy, certain protozoan infestations, and in the repair phase following infections.

IV. THE SIGNIFICANCE OF THE MYELOID MATURATION CURVE. The myeloid maturation curve may be defined as the curve produced by drawing a line through the average numbers of the different cell types of the myeloid series from the myeloblast through the successive stages of maturation to the polymorphonuclear filamentous cell.* Under ordinary circumstances, the curve normally progresses by relatively regular increments to a peak at the polymorphonuclear non-filament stage and tends to drop appreciably thereafter. Thus the values obtained for the myeloid maturation curve in material obtained from the sternal bone marrow may be closely correlated with the Arneht or Schilling indices in the peripheral blood. The only condition producing a consistent shift of the myeloid maturation curve to the left in the bone marrow is myeloid leukemia. On the other hand the "leukemoid" reaction affects the entire maturation curve, and quite frequently there is a tendency to shift toward the right. In myeloid leukemia the curve is definitely skewed to the left, while in the "leukemoid" reaction the curve closely resembles the normal with the exception that the total relative number of myeloid cells

is greatly increased. The "leukemoid" reaction occurs in chronic infections, such as sepsis and in some cases of tuberculosis; in lupus erythematosus, sarcoidosis and dorso-lateral sclerosis; in some cases of cirrhosis of the liver and neoplasms; and as a response to irritation of the myelopoietic tissue in the course of accelerated erythropoiesis.

It was our hope that the differential counts of material obtained by aspiration of the bone marrow would give information pathognomonic of certain disease entities involving the hematopoietic system. A careful analysis of the data presented shows that this laboratory technique adds only corroborative evidence of the presence of a given disease and only in unusual circumstances can a definite diagnosis be made based purely on the cytologic changes in the bone marrow. Therefore, observations made on the cytologic alterations of the bone marrow in any given case must be interpreted in terms of the clinical findings.

Summary. 1. Differential counts of material aspirated from the sternal bone marrow were performed on 6 normal individuals and on 148 diseased individuals whose illnesses were classified into 24 categories.

2. The *mean* normal values which were used as a base line for determining significant deviations from the normal compare favorably with data obtained from other observers whose techniques were comparable.

3. Significant deviations from the *mean* normal values were noted in myeloid, lymphatic and monocytic leukemias, lymphosarcoma, plasma cell myeloma and in conditions causing active regeneration of erythropoietic tissue such as pernicious anemia, secondary anemia and congenital hemolytic icterus.

4. Diagnostic significance may be attached to the presence of increased numbers of monocytes, megablasts, or plasma cells in material aspirated from the sternal

* For purposes of calculation of the myeloid maturation curve, the absolute values for the various cell types were based upon 100 myeloid cells.

LUCIA, HUNT: THE MYELOID MATURATION CURVE

bone marrow. These cell types occur so rarely in normal bone marrow that their presence, in all probability, indicates an important lead to the accurate diagnosis of the limited number of diseases in which they occur. A marked increase in monocytes and in primitive unclassified cells (histiocytes) occurs in monocytic leukemia; a similar increase in megaloblasts is diagnostic of pernicious anemia; appreciable increases in lymphocytes occur in lymphatic leukemia and in lymphosarcoma; and an incidence of plasma cells greater than 6% in the bone marrow may be regarded as diagnostic of plasma cell myeloma.

5. An increased number of normoblasts indicates stimulation of erythropoiesis but is not diagnostic of any specific disease condition.

6. An increase of eosinophils occurs in the bone marrow in allergy, certain protozoan infestations, in the repair phase following infections, and in diseases characterized by fibrotic alteration of the marrow.

7. In myeloid leukemia there is a definite shift of the myeloid maturation curve to the left, the promyelocytic cells showing the greatest change. These findings are confirmatory but not specifically diagnostic of myeloid leukemia.

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TREATMENT OF PERNICIOUS ANEMIA WITH SYNTHETIC L. CASEI FACTOR

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WITH the synthesis of the *L. casei* factor from liver in 1945,¹ this newest member of the water-soluble vitamins became available in adequate supply for clinical trial. The exact relationship of this material to the folic acid from spinach of Mitchell, Snell and Williams,¹⁹ by which name it is popularly known, vitamin Bc,²³ vitamin M,^{10,11,12} the norite eluate factor,^{16,26} *S. lactis* R and *S. lactis* U factors,³¹ remains to be established. Certain similarities are apparent in their biologic characteristics. Their close chemical relationship is indicated in the recent report of the chemical structures of the *L. casei* factors from liver and an *S. lactis* factor,² which differ from each other only in that the former contains a molecule of glutamic acid. This problem has been fully discussed elsewhere, and will not be considered further here.^{4,6,22,34}

The observation that the leukopenia produced in monkeys and rats on deficient diets could be corrected by the *L. casei* factor^{12,15,17} led to its clinical trial in patients with leukopenia from various causes. Most reports on the treatment of granulocytopenia are unfavorable, but Watson *et al.*³³ report good results in cases of granulocytopenia due to Roentgen therapy. Berry *et al.*³ report leukocyte responses in 5 malnourished patients with leukopenia.

The similarity between the sprue syndrome in man and vitamin M deficiency in monkeys which had been successfully treated by Day *et al.*¹² with folic acid led Darby^{7,8,9} and Spies^{28,30} and their collaborators to exhibit the newly available

synthetic *L. casei* factor in a number of patients with sprue with excellent results, including a favorable hematologic response.

Darby and Jones⁷ treated 2 cases of sprue with macrocytic anemia with 15 mg. synthetic folic acid intramuscularly daily. Glossitis disappeared on the 4th day. Reticulocyte peaks of 15.3% and 16.1% were attained on the 9th day and 4th day respectively. Darby, Jones and Johnson^{8,9} reported similar results in 3 more cases of sprue with reticulocyte peaks of 11 to 43% on the 6th to 8th days of treatment with 15 mg. folic acid intramuscularly daily. Hemoglobin, red cell and white cell count rises followed. The diarrhea and impaired absorption showed improvement. They calculated⁹ that the maintenance dose of folic acid would be 0.1 to 0.2 mg. daily, while therapeutic dosage would be in the vicinity of 1 mg. per day. This deduction was based not on clinical study but on the fact that the chick requirement for the *L. casei* factor was one-fifth to one-tenth that for riboflavin. Spies *et al.*³⁰ treated 3 patients with sprue and macrocytic anemia with folic acid, 100 mg. twice daily by mouth, with a reticulocyte response on the 4th to 5th day, reaching a peak of 17.2 to 22.7% on the 6th to 7th day. Three other patients who did not respond significantly to 5 mg. daily, responded fairly satisfactorily to 10 mg. daily. Similar hematologic and clinical improvement was reported by Spies and his group²⁸ in 9 such patients, who were treated with 10 to 200 mg. folic acid daily.

* Since this paper was submitted, we have treated one patient with Addisonian pernicious anemia with 1.25 mg. folic acid daily by mouth. The initial hemoglobin was 50 per cent and the red count 2.3 million. On the eighth day of therapy, a reticulocyte peak of 5.0 per cent was attained. No second response occurred when the dosage was increased to 2.5 mg. On the twenty-fourth day, the hemoglobin was 72 per cent and the red count 3.7 million.

Crude folie acid concentrates (using the term generically, not in the strict sense of the compound of Mitchell, Snell and Williams¹⁹) had been tried in 1944 by Castle *et al.*⁵ and by Moore and his associates²⁰ in the treatment of pernicious anemia without response. Sharp and his associates²⁵ in 1944 treated 10 patients with refractory anemia, including pernicious anemia, with vitamin Be yeast concentrate, with increase in red cell volume; but Watson³³ had found it ineffective in "refractory anemia." In November 1945, Spies and his co-workers²⁷ reported the first favorable response of patients with macrocytic anemias to synthetic folie acid. They treated 5 patients with 20 to 50 mg. daily intramuscularly, while the diet was controlled to exclude meat and meat products. In 3 to 4 days definite subjective improvement was noted. The reticulocyte response began on the 3rd to 8th day and reached a peak of 6.5 to 14.5% between the 5th and 10th days. Another group of 4 patients was treated with 50 to 100 mg. daily by mouth with similar effect. Vilter, Spies and Koeh³² reported the successful treatment of 14 cases of macrocytic anemia, including nutritional and Addisonian anemias, with synthetic folie acid. In 5 of the 6 patients with leukopenia in addition to anemia, the white blood count rose under treatment. Pellagrous glossitis healed in 4 to 10 days, and burning of the tongue without objective glossitis cleared in the same interval. The onset of remission was accompanied by marked increase in appetite in most patients. In 2 cases with neuromuscular complaints, there was incomplete relief of paresthesia. The authors believed that the response was submaximal in that only 6 of 14 patients attained a hemoglobin level of 12 gm. % and 1 had a second reticulocyte response when treated with 50 U.S.P. units reticulogen after 18 days of *L. casei* factor, 20 mg. intramuscularly, daily. The longest period of treatment was 30 days and the dosage varied from 20 mg. daily parenterally to 150 mg. daily by mouth. Moore and his associates²¹ treat-

ed 4 patients with macrocytic anemia, including 2 with Addisonian pernicious anemia, with folie acid. On the 3rd day of treatment with 100 mg. orally daily, subjective improvement was noted. The reticulocyte response began on the 4th day and reached a peak of 40% on the 7th day. Treatment was continued for 10 days, at which time the red blood count was slightly over 3 million. They concluded that this form of therapy was insufficient for a complete hematologic response. They treated 2 other patients with 2 mg. folie acid intravenously with what was interpreted as a submaximal response.

Spies²⁹ reported the successful treatment of a group of 26 cases of macrocytic anemia of various types with folie acid in doses of 10 mg. or more daily. Subjective improvement was noted on the 3rd day, and the reticulocyte response began on the 3rd to 6th day, reaching a peak of 6.4 to 31.8% on the 6th to 8th day. All elements in the peripheral blood tended to return to normal. He noted that on this therapy, the megaloblasts in the bone marrow decreased. Spies and his collaborators³⁰ concluded that folie acid was effective in the treatment of Addisonian pernicious anemia, nutritional macrocytic anemia, the macrocytic anemias of sprue, pellagra and pregnancy. However, the response to yeast and liver extract seemed to be out of proportion to their folie acid content. A number of patients who failed to respond to 3 to 4 mg. folie acid by mouth, responded to liver extract calculated to contain 1 mg. or less of folie acid daily.²⁹ The highest red blood count attained was 4.22 million with a hemoglobin level of 13.9 gm. per 100 cc. in a patient with an initial count of 2.01 million and hemoglobin level of 8.3 gm. per 100 cc., who received 100 mg. of folie acid by mouth daily for 40 days. Doan and his associates¹³ treated 1 patient with pernicious anemia and combined sclerosis of the cord with 2 mg. folie acid parenterally for 15 days with results indistinguishable from those which would have been

expected with parenteral liver. No secondary reticulocyte response occurred when the dose was increased to 10 mg. daily. On the 10th day of therapy, the sternal marrow appeared normal. The maximum reticulocyte response of 26.8% was reached on the 15th day. On the 40th day of treatment, the red blood count was 4 million per c.mm. and the hemoglobin 13 gm. per 100 cc. (initial levels 1.49 million and 5.8 gm.). On the 2nd day of treatment, the patient's paresthesias disappeared and on the 21st day vibratory sensation and the Romberg test reverted to normal.

Zuelzer^{35,36} stated that folic acid is a specific anti-anemic factor the lack of which results in megaloblastic dysplasia of the bone marrow elements and macrocytic anemia. He described an anemia of children, hematologically indistinguishable from pernicious anemia, although not constantly associated with achlorhydria, which responded to treatment with folic acid in doses of 5 to 20 mg. intramuscularly or 50 to 100 mg. orally daily for 1 to 3 weeks. When achlorhydria was noted before treatment, it cleared on this regimen. Both the bone marrow and peripheral blood returned to normal. The response to folic acid was indistinguishable from that to liver, and no second reticulocyte response could be obtained with one, after the other had been exhibited. Within 2 days of the inception of therapy, the bone marrow showed complete disappearance of the megaloblastic pattern. Children with other types of anemia had no response to folic acid.

It is interesting to note that a potent antipernicious anemia fraction of liver is effective neither in the treatment of vitamin M deficiency in monkeys¹¹ nor the vitamin B₁₂ deficiency of chicks.³⁴ It has therefore been concluded that *L. casei* factor and the antipernicious anemia principle are different.³⁴ It may be more accurate to conclude that the antipernicious anemia principle is not a single factor, since folic acid does appear to be an effective antipernicious anemia factor. It may also be postulated that the erythro-

cyte maturation factor is folic acid or is synthesized by the human organism from folic acid. Other compounds with similar structure or conjugation compounds of folic acid may also be utilized in the synthesis of the erythrocyte maturation factor by the human organism, without having folic acid activity for other organisms. Thus, both the *L. casei* factor and the *S. lactis* factor,² the similarity of whose structure has been mentioned previously, are potent in promoting the growth of *S. lactis*, while only the former is potent for *L. casei*. The antipernicious anemia potency of the *S. lactis* factor remains to be determined.

Method. We have undertaken to study the therapeutic effect of synthetic folic acid* in the treatment of pernicious anemia. In addition, we attempted to determine the dosage which might be considered equivalent to a unit of liver (i. e., the minimal dose which, when given daily by mouth, produces a maximal hematologic response). In the first group of patients (4 cases), we gave oral doses which in the experience of others had produced satisfactory effects. After we had established the efficacy of this therapy, the succeeding patients were treated with a dose that was expected to produce a sub-maximal response so that a second reticulocyte response might be tested for with increased doses¹⁵ (3 patients).

Daily reticulocyte counts were performed by the method of drawing blood smears on slides previously coated with alcoholic brilliant cresyl blue. Hemoglobin determinations were made with a Sahli-Hellige hemoglobinometer in which 100% equals 17 gm. per 100 cc. Red cell, white cell and platelet counts were performed in the Neubauer counting chamber. The red cell volume was determined in the Wintrobe hematocrit on oxalated blood.

Case Histories. CASE 1. M. E., a 76 year old woman, complained of dyspnea, weakness, dizziness, numbness of her feet, precordial pain and palpitation of 2 weeks duration. She had become gray at the age of 30. She was told that she was anemic 25 years before, but no therapy was attempted. Physical examination revealed a well-developed and well-nourished pale old woman. The physical and neurologic exam-

ination was entirely negative except for pallor. Gastric analysis revealed achlorhydria, refractory to histamine. Gastrointestinal Roentgen ray series revealed no abnormality. Sternal marrow showed 3 to 4% megaloblasts on admission and 0.6%

remained at about this level. The mean corpuscular volume was 125 μ on admission and 99 μ after 1 month of treatment. The platelet count was 130,000 per c.mm. on admission and 290,000 on the 13th day of treatment. Throughout her hospital stay,

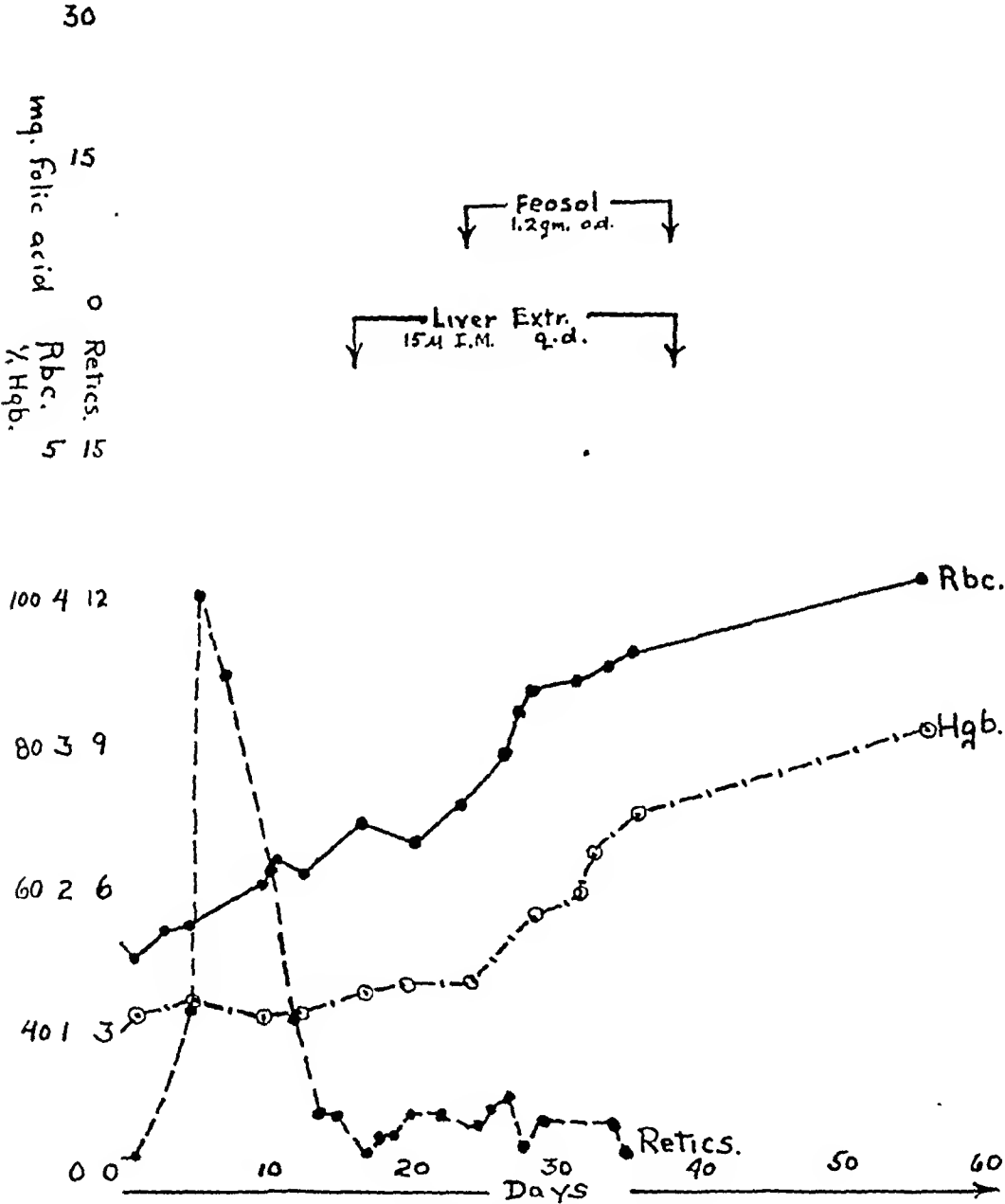


FIG. 1.—Hematologic response in Case 1.

megaloblasts after 2 weeks of therapy. The treatment with folic acid and later liver, and the hematologic response are described in Figure 1. Not shown is the white count, which rose from an initial level of 5000 per c.mm. to 11,000 while on folic acid, and

she ran a low grade fever, always below 100° F. except between the 8th and 19th day when it was between 100° and 101.8° F. (peak on 12th and 13th days). There was only a slight upper respiratory infection to account for the fever. On the 8th and 9th

days of treatment, the nurse's notes revealed improved appetite.

CASE 2.—I. F., a 70 year old man, complained of fatigue for 1 year, slight icterus for 2 days. He had experienced an attack of gall bladder colic 4 years before admission, but no pain was associated with the present episode. The dietary history revealed poor protein and vitamin intake. Temperature on admission was 102° F. but subsided during the 1st week and remained normal thereafter. The liver was felt 2 finger-breadths below the costal margin and the spleen 1 finger-breadth. There was tenderness in the right upper quadrant. There was no glossitis and the neurologic examination was negative. Erythrocyte sedimentation rate was 76 mm. in 1 hour, icterus index 15, bilirubin 2.9 mg. % with delayed direct van den Bergh reaction. On the 3rd hospital day the icterus index was 9 and the bilirubin 1 mg. % respectively; and on the 5th hospital day the bilirubin was 0.5 mg. % and the direct van den Bergh negative. Alkaline phosphatase was 21 King-Armstrong units. The cephalin flocculation test was negative. Gall bladder Roentgen series revealed no filling of the gall bladder. Gastric analysis revealed no free acid after histamine both before and after completion of treatment. Gastro-intestinal Roentgen ray series revealed no abnormality. The bone marrow before treatment revealed the typical megaloblastic marrow (4%) of pernicious anemia. The hematologic response to folic acid therapy is shown in Figure 2. As noted, there was a reticulocyte crisis before the inception of folic acid treatment and a second response to the drug. This is discussed below. The white blood count rose from 2200 on admission to 5500 on the day specific treatment was begun, and remained at about this level. The platelet count was 290,000 before treatment and did not change significantly. The mean corpuscular volume was 110 μ at the onset of therapy and fell to 95 at the time of discharge (7 weeks after admission).

CASE 3. C. P., a 64 year old Italian laborer, was admitted for the first time in September 1945 for epigastric burning, anorexia and weakness of 3 months duration. Gastro-intestinal series at that time was negative; gastric analysis revealed achlorhydria. Gastroscopy revealed marked atrophic gastritis. Bone marrow aspiration disclosed a typical megaloblastic marrow

(5%). The hemoglobin was 59% and the red blood count 2.7 million. On yeast (60 gm. daily for 5 days) and liver extract (15 days), the hemoglobin rose to 78% and the red blood count to 3.66 million, but no reticulocyte response was noted.

Upon discharge in October 1945, the patient discontinued all therapy. He was readmitted March 1946 complaining of epigastric distress, anorexia, diarrhea, weakness and numbness of the fingers for 1 month. Examination revealed that the liver extended 3 finger-breadths below the costal margin. The spleen was felt 1 finger-breadth below the costal margin. There was moderate atrophic glossitis. Position sense was intact in the hands and feet but vibratory sense was diminished over the right tibia. Erythrocyte sedimentation rate was 30 mm. in 1 hour. Icterus index was 8, bilirubin 1.2 mg. % and the direct van den Bergh negative. There was gastric achlorhydria after histamine. Bone marrow aspiration again revealed a typically megaloblastic marrow. After 3 days of folic acid treatment the gastro-intestinal symptoms subsided and the patient noted marked improvement in appetite. Gastroscopy, performed after 15 days of therapy, revealed much less marked atrophy than was noted at the time of the first admission. Bone marrow aspiration performed 2 weeks after the onset of treatment revealed no megaloblasts, 59% normoblasts and 7% erythroblasts. Two weeks after admission, he noted disappearance of the complaint of numbness in his fingers. At the same time, the papillae of his tongue began to regenerate, and the tongue became normal within 1 month. After treatment for 2½ months, the patient complained of stiffness and numbness of his hands, but there was no change in reflexes or proprioceptive sensation in upper or lower extremities. One month later, at which time his red blood count was 5.2 million and his weight was 151 pounds as compared to 140 on admission, he complained of increasing numbness in his hands and weakness in his knees. He stated that he had difficulty in buttoning his vest and tying his shoe-laces. There was suggestive minimal diminution in vibratory sensation at the right ankle, but no other change. He consulted another physician who treated him with liver extract and vitamin B complex intramuscularly. After the third injection, over a period of

2 weeks, he noted marked improvement in the numbness of his fingers, was again able to perform precise acts. When seen again 1 month after the induction of liver and vitamin B therapy, at which time he had received 6 injections, he had no complaints,

ment), is shown in Figure 3. The platelet count rose from 50,000 to 180,000 per c.mm. during treatment. The mean corpuscular volume was 158 $c\mu$ on admission, 110 $c\mu$ on the 14th day of treatment. It was not repeated again.

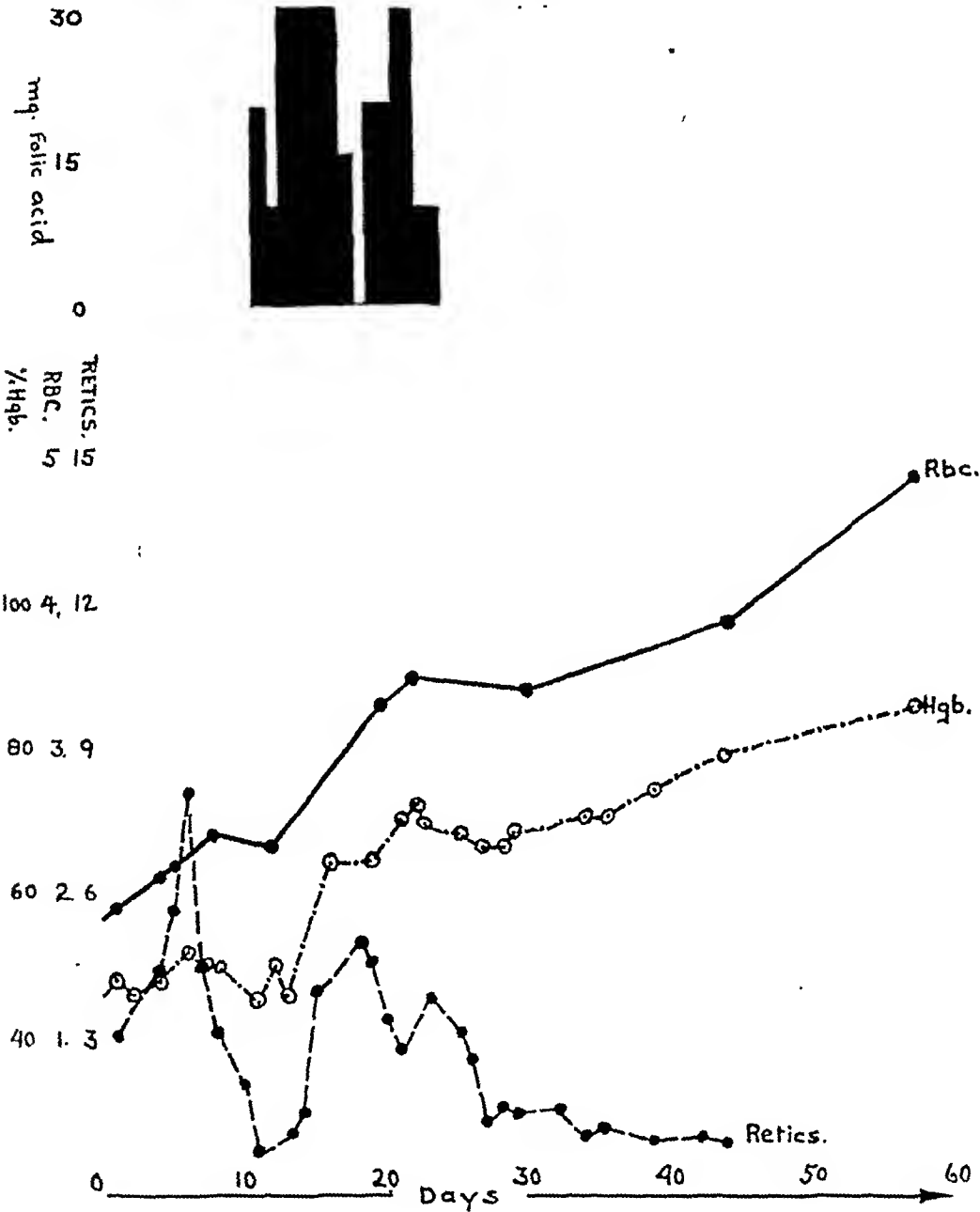


FIG. 2.—Hematologic response in Case 2.

but his neurologic findings, as before, showed slight impairment of vibratory sensation at the ankles.

The hematologic response to folic acid therapy, except for the white count, which rose from 4000 to 8000 (after 2 weeks treat-

CASE 4. O. S., a 67 year old Jewish woman, gave a 2 year history of epigastric and abdominal discomfort and weight loss. During the 2 months preceding admission her symptoms had become aggravated, associated with weakness, shortness of breath,

constipation and a loss of 10 pounds in weight. There was no glossitis. Liver and spleen were not palpable. Neurologic examination was negative except for slight diminution in vibratory sense at the knees and ankles. Erythrocyte sedimentation rate was 30 mm. in 1 hour. Gastric analysis revealed achlorhydria after histamine. The stools were persistently guaiac negative. The Gastro-intestinal series and barium enema were negative. The bone marrow revealed 6.4% megaloblasts, 32% normoblasts, 0.8%

5700 after 2 weeks treatment. Figure 4 describes the hematologic response. The only neurologic abnormality, diminished vibratory sensation in the legs, was slightly improved by treatment, in that after 2 months it became normal at the knees and was only slightly diminished at the ankles. Her weight increased from 108 pounds on admission to 116 in 2 months.

CASE 5. M. F., a 71 year old Irish woman, had noted weakness, fatigue, anorexia and weight loss 5 years before admission for

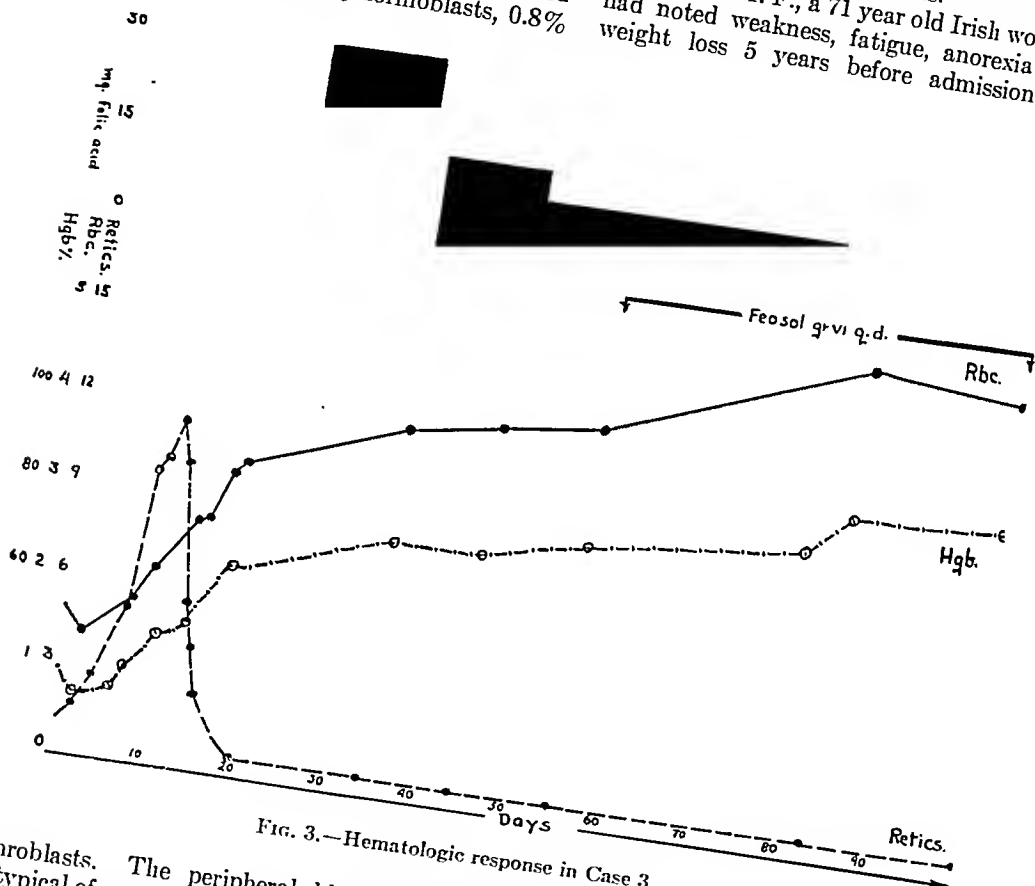


FIG. 3.—Hematologic response in Case 3.

erythroblasts. The peripheral blood was also typical of pernicious anemia. The mean corpuscular volume was 135 μ .

The patient noted marked improvement in appetite on the 5th day of therapy with 20 to 30 mg. folic acid daily, and her appetite became insatiable about the 7th day of treatment. Bone marrow aspiration on the 15th day of treatment revealed an active, essentially normal marrow, without megaloblasts. Platelets rose from 60,000 per c.mm. on admission to 230,000, 1 month later. White blood count was 3000 on admission,

which she received sporadic injections of liver extract with slight improvement. She had received no treatment for 2 years, and for 6 months had noted the return of these symptoms associated with numbness of hands and feet so that walking became increasingly difficult. She had been bed-ridden for 1 month prior to admission.

On admission, the positive physical findings were marked pallor with a *cafe-au-lait* complexion, retinal hemorrhage and exudates, atrophic glossitis, sclerosis of peripheral pulses, impaired position and vibratory

sense in hands and feet, astereognosis, impaired pin-prick and light touch sensation in hands, active knee jerks (left more active than right), bilaterally positive Babinski's sign. Stool guaiac was negative, erythrocyte sedimentation rate 65 mm. in 1 hour. Gastric achlorhydria refractory to histamine was noted. Sternal marrow aspiration yielded an active megaloblastic marrow (16.8% megaloblasts).

By the 10th day of treatment, the patient stated that she was watching the clock for meal time and that the paresthesias in her fingers had improved. By the 22nd day, she stated that the paresthesias had disappeared entirely. The knee jerks were now equal and active and the Babinski reflexes had disappeared. Sensation in the upper extremities appeared to be normal. On the 30th day, she left her bed for the first time

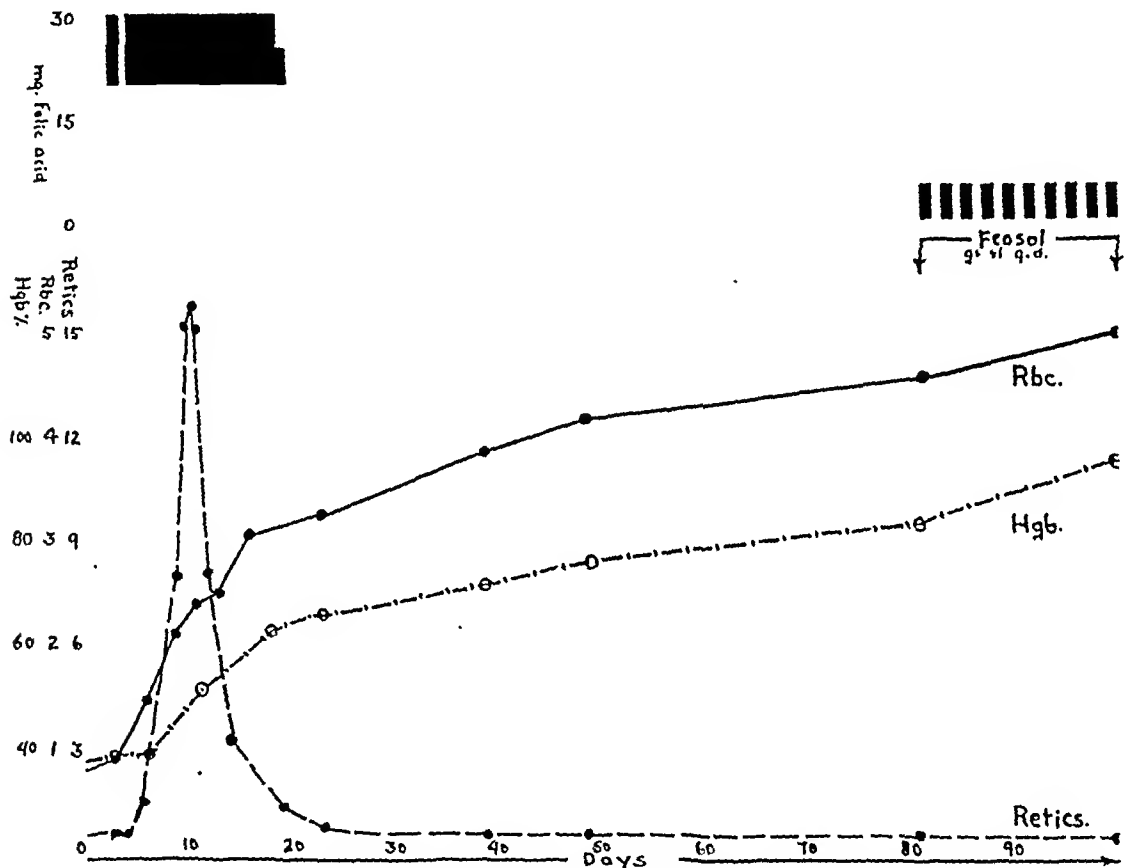


FIG. 4. Hematologic response in Case 4.

She was treated with 5 mg. folic acid daily until the reticulocyte response had subsided, after which the dose was increased to 10 and then 30 mg. daily. On the 3rd day of therapy, improvement in appetite was noted. Bone marrow aspirated on the 4th day revealed 4% megaloblasts, which were considered atypical in that the nuclei stained more deeply, suggesting transition to erythroblasts. On the 6th day of treatment, new papillae were noted on the tongue which began to feel rough to the touch. On the 8th day of treatment, only rare megaloblasts could be found in the marrow smears and on the 38th day there was none.

and began to exercise in a walker. However, about 2 weeks later, she began to show signs of mental deterioration, complained of pains in her legs and refused to leave her bed. The objective neurologic findings remained static. She developed decubitus ulcers followed by a left lower lobe pneumonia with temperature up to 107° F. Urinary and fecal incontinence, which had been noted on admission and had improved during therapy, recurred. She died on the 4th day of the acute illness. Postmortem examination was not obtained.

Her hematologic response to physical therapy is shown in Figure 5. Not shown

are the rises in platelet count from 100,000 to 280,000 and in white count from 2000 to 6000 before the onset of pneumonia, when it rose to 10,000. The initial mean corpuscular volume was 118 μ .

insomnia. She complained of constant coldness of hands and feet, and noted considerable weight loss. For the past several months she had been treated with iron without effect.

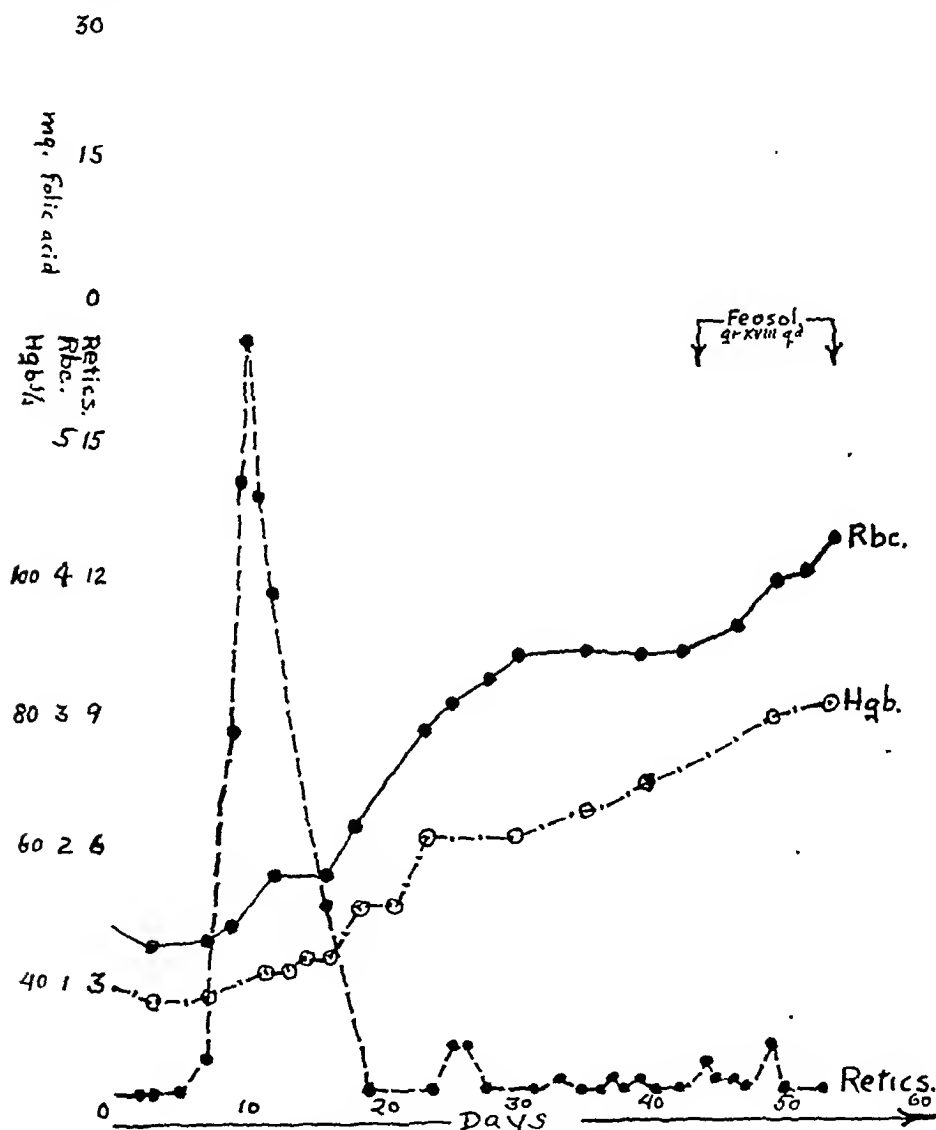


FIG. 5.—Hematologic response in Case 5.

CASE 6. P. M., a 59 year old Polish woman, had been in good health until 8 months before admission when she had an attack of gall bladder colic. The patient had always avoided fried and fatty foods, but restricted her diet more carefully following this episode. For the past 8 months she had noted anorexia, constipation and

Physical examination revealed lemon-yellow skin and sclerae. The fundi showed marked arteriolar narrowing and numerous petechial hemorrhages. The tongue was smooth and atrophic. Blood pressure was 110/64. There was marked sclerosis of the peripheral pulses. The deep tendon re-

flexes were equal and active. There was no impairment of vibratory or position sense.

The peripheral blood was typical of pernicious anemia: hemoglobin 32%, red blood count 1.2 million, white blood count 3500 with many hypermature neutrophils; there were marked poikilocytosis and anisocytosis, and a few megaloblasts and rare myelocytes were seen. Mean corpuscular volume was 120 μ . Urinary urobilinogen was demonstrable in a dilution of 1:20. Stool guaiac was negative. Gastric achlorhydria refractory to histamine was noted before and after treatment. The bone marrow revealed 14.8% megaloblasts.

On the 8th day, new papillæ were noted in the central portion of the tongue. On the 16th day of treatment, she developed right upper quadrant pain with spasm and tenderness and fever to 103° F. These symptoms subsided after 7 days. A gall bladder Roentgen ray series failed to visualize the gall bladder, confirming the impression of acute cholecystitis. Following the subsidence of this episode, the patient again began to show subjective and objective improvement, followed by a second reticulocyte response to 2.5 mg. folic acid as shown in Figure 6. After this reticulocyte response manifested itself, she was permitted a regu-

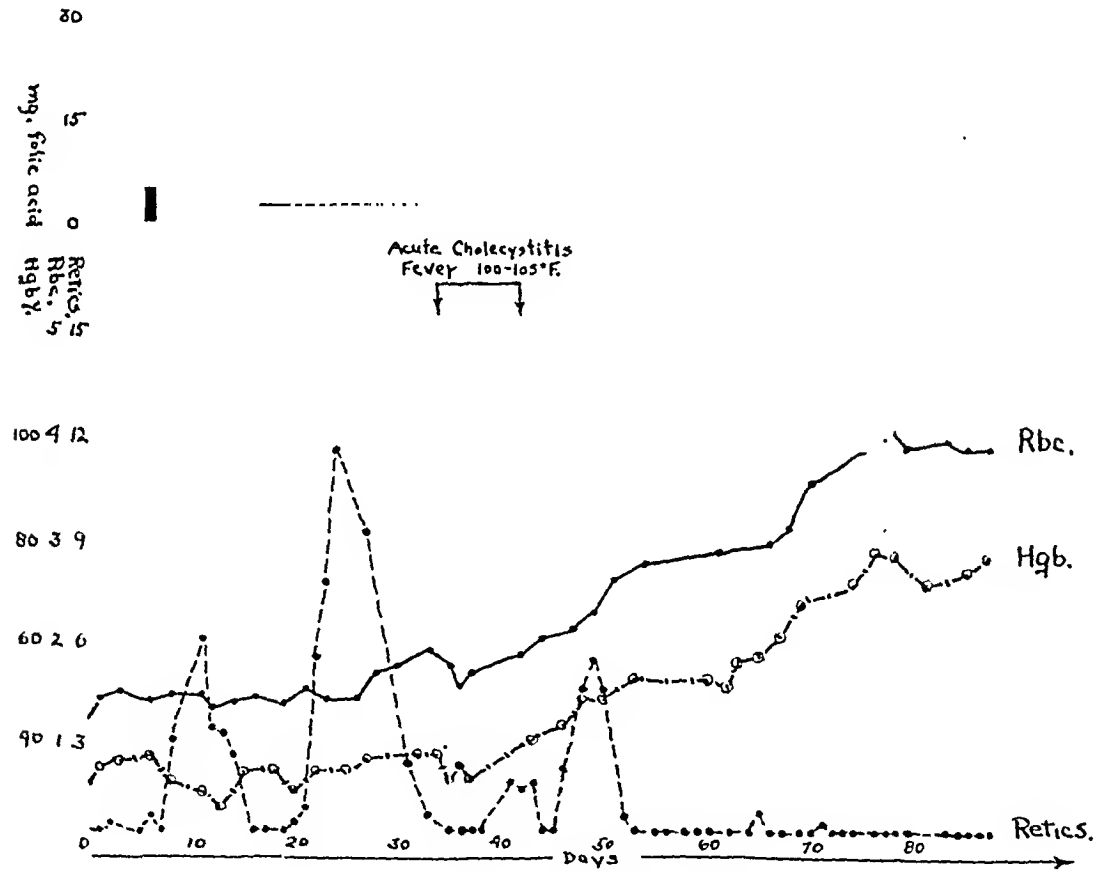


FIG. 6.—Hematologic response in Case 6.

The patient was placed on a diet restricted in sources of extrinsic factor and received a single dose of 5 mg. folic acid by mouth with reticulocyte response shown in Figure 6, but no subjective improvement. After the subsidence of this response, she was treated with 2.5 mg. folic acid daily. On the 4th day of this regimen she felt stronger, looked brighter, and stated that her appetite was considerably improved.

lar, low fat diet, without restriction of extrinsic factor. When this response subsided, the dose of folic acid was increased to 30 mg. daily by mouth without secondary reticulocyte response (Fig. 6). The fundi and tongue appeared normal when reexamined 2 months after admission. The neurologic examination remained normal throughout the period of observation. The white blood count rose from 3500 to 5000

(8300 during febrile episode) and the platelets from 100,000 to 240,000 in the 1st month. The mean corpuscular volume was 120 μ on the 19th day of treatment with 2.5 mg. folic acid daily and 90 on the 40th day of continuous therapy.

negative. Physical examination revealed a pale, chronically ill male, appearing younger than his stated age. He was not dyspneic or orthopneic at rest. The fundi revealed arteriolar narrowing, arteriovenous crossing defects, numerous hemorrhages and exu-

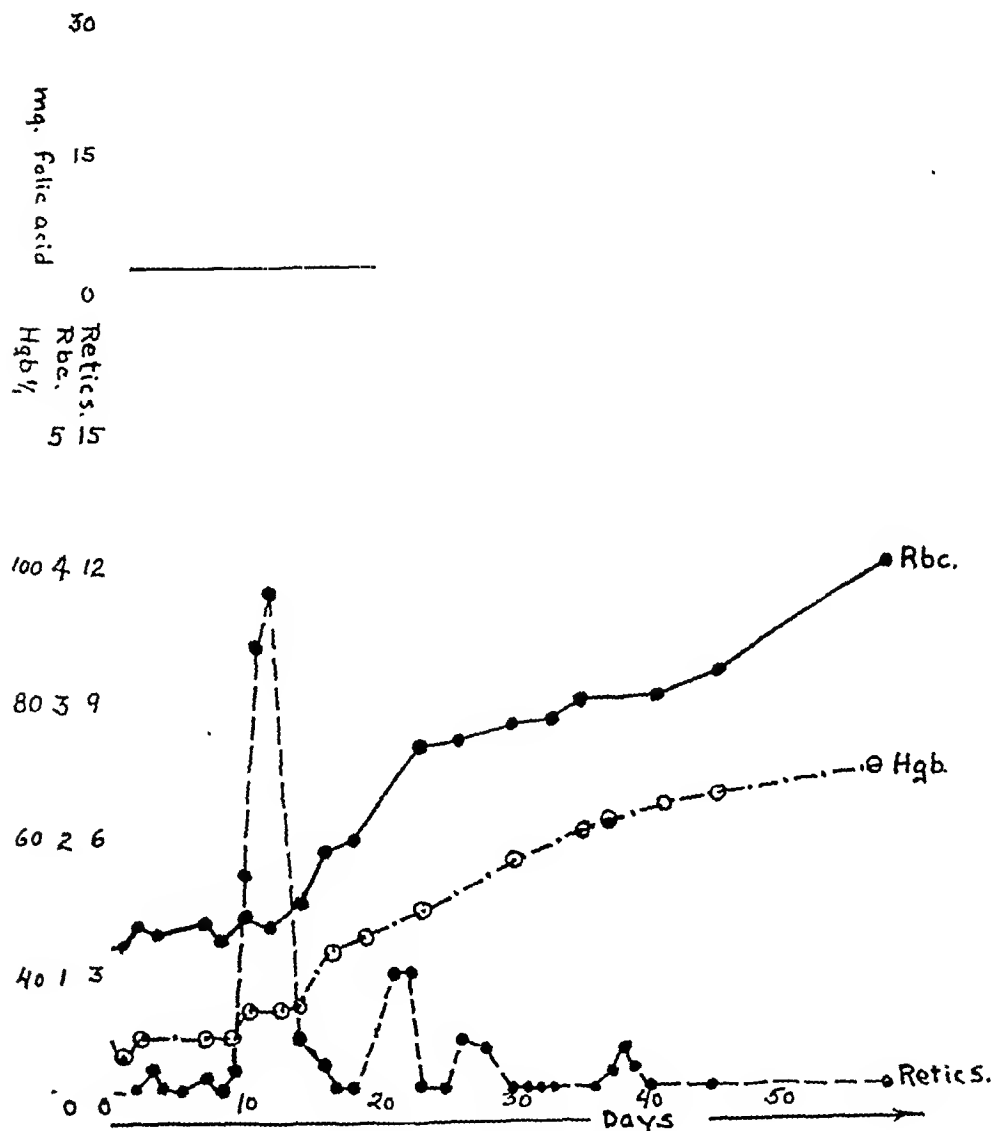


FIG. 7.—Hematologic response in Case 7

CASE 7. J. M., a 70 year old Jewish man, complained of exertional dyspnea, sub-sternal oppression, orthopnea and anorexia of 6 months duration. Gastro-intestinal series, barium enema and chest plate made 3 weeks before admission were reported as

dates. There was no cardiac enlargement. A blowing systolic murmur was audible at the apex. The blood pressure was 125/60. The liver was palpable 1 finger-breadth below the costal margin. There was no glossitis or neurologic abnormality.

On admission, the peripheral blood smear revealed marked anisocytosis, poikilocytosis, 2 nucleated red cells per 100 white cells, reduced platelets (100,000 per c.mm.). The admission white blood count was 4400 with normal differential and many hypermature neutrophils. The bone marrow was typically megaloblastic. Gastric achlorhydria persisted after histamine. The icterus index was 12, bilirubin 1.4 mg. per 100 cc., direct van den Bergh negative and total protein 6.4 gm./100 cc. Urinary urobilinogen was positive in a dilution of 1:20.

The platelet count rose from 110,000 to 210,000 at the end of 2 weeks of treatment and the white blood count from 4450 to 7100. Treatment was begun with 2.5 mg. folic acid by mouth daily and increased to 30 mg. daily after subsidence of the reticulocyte response. The hematologic response is shown in Figure 7. On the 4th day of treatment, the patient noted increased strength, improved appetite and a sense of well-being. By the 55th day of treatment, he had gained 15 pounds.

In addition to the above 7 cases of pernicious anemia, 1 case of Hodgkin's disease with postradiation leukopenia, 1 ulcerative enterocolitis with hypochromic anemia, 1 aleukemic myelogenous leukemia, 2 patients with steatorrhea without anemia and 1 patient with regional ileitis were treated with 30 to 45 mg. folic acid by mouth daily without clinical or hematologic response.

Discussion. It is apparent from examination of the hematologic responses obtained (Figs. 1 to 7) that synthetic *L. casei* factor from liver is capable of producing a remission in patients with Addisonian pernicious anemia in relapse. In each case subjective improvement in appetite and general well-being was manifest about the 4th day of treatment. When gastrointestinal symptoms such as epigastric distress, anorexia or diarrhea were present, these subsided within a week. Glossitis disappeared in the same period, associated with beginning regeneration of papillae. The reticulocyte response became manifest between the 3rd and 7th days and reached its peak between the 7th and 10th days.

Leukopenia and thrombocytopenia disappeared. Achlorhydria was not modified. Neurologic complications, when present, were usually only minimally improved, but no progression was noted.

In Case 1, no secondary reticulocyte response was obtained to 15 units liver extract daily intramuscularly following 20 to 30 mg. folic acid daily by mouth. This indicated that the dosage of folic acid exhibited had produced a maximal hematologic response.¹⁸ The hemoglobin and red cell rise was sluggish. The addition of iron resulted in a prompt response. This phenomenon was noted in other cases treated with folic acid, in which the hemoglobin became stabilized, usually at about 70% (11.9 gm./100 cc.) with a color index of 1 or less: upon the addition of iron to the regimen, the hemoglobin rose to normal values (Cases 3, 4 and 5).

In Case 2, there was a spontaneous reticulocyte crisis, probably related to the subsidence of the acute cholecystitis and the ingestion of an adequate diet. The patient's diet had previously been inadequate in protein foods. This response, however, was submaximal, since after its subsidence 20 to 30 mg. per day of folic acid produced a second reticulocyte response. The second response reached a peak of 5% reticulocytes on the 8th day of folic acid. The low peak can be ascribed to the fact that there had been a previous submaximal response of 8%.

Cases 3 and 4 illustrate the attainment of normal hemoglobin levels (over 85%—over 14.5 gm. per 100 cc.) with folic acid and iron over extended periods (2½ months of folic acid). The maintenance dose used in each case was 5 mg. orally daily.

In Case 6, a single oral dose of 5 mg. of folic acid produced a reticulocyte peak of 6% on the 6th day, which was not followed by a significant hemoglobin or red cell rise. After this reticulocyte response had subsided, 2.5 mg. folic acid daily produced a second reticulocyte response with a peak of 11.6% on the 8th day, indicating that the original single dose of 5 mg. had been inadequate. The red cell

and hemoglobin response was very sluggish. After the acute cholecystitis with fever up to 103° F. subsided, a further slight reticulocyte response occurred on the same dose of folic acid, without change in diet, and the hemoglobin and red cell count began to rise significantly. This would appear to indicate that in the face of the acute infection, 2.5 mg. of folic acid daily had produced a submaximal response, while the same therapy was adequate in the absence of intercurrent disease (as indicated by the lack of an additional reticulocyte response on an improved diet and increased folic acid dosage).

Cases 5 and 7 showed straightforward hematologic responses to 5 mg. and 2.5 mg. folic acid daily, respectively, with no further reticulocyte response to increased dosage.

It will be noted that the observed reticulocyte response fell short by about 50% of the expected response. However, this may be attributed to the method, since Minot and Castle's curves¹⁸ are based on the determination of reticulocytes on smears made after the blood has been mixed with an aqueous solution of brilliant cresyl blue. The slide technique used in our laboratory gives considerably lower levels (*cf.* normal of less than 0.5% with normal of 1 to 1.5%). The erythrocyte response compares favorably with that obtained with liver.¹⁴

Conclusions. We may conclude that synthetic *L. casei* factor from liver is a potent antipernicious anemia factor, effective in producing a complete hematologic response, including reticulocyte count, red cell count, white cell count and platelet

TABLE 1.—THE INITIAL RED COUNTS, CALCULATED EXPECTED RETICULOCYTE RESPONSE FOR ORAL LIVER AND NOTED RESPONSE

Patient	Initial R.B.C.	Calculated reticulocytes	Found reticulocytes
I. M. E.	1 6	20 4	12
II. I. F.	1 8	17 1	8, 5
III. C. P.	1 5	22 3	11
IV. O. S.	0 9	38 0	15
V. M. F.	1 4	24 3	17
VI. P. M.	1 3	26 5	6, 11.6
VII. J. M.	1 3	26 5	11 6

Signs of combined sclerosis of the cord were noted in 4 cases (Cases 1, 3, 4 and 5) and were severe in 1 (Case 5). In Cases 3 and 4, the disease was characterized by slight diminution of vibratory sense and paresthesias in the lower extremities, while in Case 1 there were paresthesias without objective changes. On treatment, these symptoms subsided. However, in Case 3 they returned after 2 months, while still on treatment with folic acid only to subside again with liver and vitamin B treatment. In Case 5 there was impairment of proprioceptive sense in the upper and lower extremities, and of motor power in the lower. The findings in the arms cleared under treatment, but those in the legs improved only minimally. There was no progression in the neurologic findings, but the patient developed a senile psychosis followed by a fatal bronchopneumonia.

count, and correction of the megaloblastic dysplasia of the bone marrow. Reticulocytosis began between the 4th and 7th days and reached a peak 2 to 4 days later. As noted by other workers, subjective improvement, most strikingly evidenced by greatly improved appetite, occurred usually on the 3rd or 4th day of treatment. Glossitis and other gastro-intestinal symptoms subsided within 1 week, and regeneration of papillae became apparent at this time. The minimal therapeutic dose, corresponding to one U. S. P. unit of liver is 2.5 mg. or less daily by mouth, since no second reticulocyte response could be produced in the 2 patients maintained on this dosage, by increasing the amount of folic acid. As with liver, larger doses are required in the face of infection. The failure of liver extract to produce a second response in 1 patient treated with 30 mg.

of folic acid daily indicates that folic acid is capable of producing as complete a hematologic response as liver. By the addition of iron, the red cell count could be raised to normal levels on folic acid alone, given over a sufficiently long period (2 to 3 months). These results are at variance with those of Moore²¹ and Vilter²² and their co-workers, who failed to obtain complete remissions with folic acid. However, premature discontinuance of therapy may account for their inadequate response to folic acid. Combined sclerosis of the spinal cord was improved only very slightly by folic acid treatment. However, no case of development or progression of the neurologic disease during therapy was noted. In this respect, the experience is similar to that with liver. In the 1 case (Case 3) in which minor paresthesias recurred during treatment and again subsided on liver and vitamin B injections, evaluation is difficult because of the lack of objective changes and the confusion of the experiment by the administration of both vitamin B and liver extract.

Folic acid did not prove effective in the treatment of anemia and leukopenia due to acute myelogenous leukemia (leukemic) or Hodgkin's disease, nor did it influence non-specific disease of the small bowel or colon.

It has been previously pointed out^{21,29,34} that the antipernicious anemia potency of liver is out of proportion to its *L. casei* factor content and that liver fractions without *L. casei* potency are very active

in erythrocyte maturation. The close chemical similarity, but microbiologic dissimilarity, between the *L. casei* factor (a compound of glutamic acid, para-amino-benzoic acid, and 2-amino-4-hydroxy-6-methyl-pteridine) and *S. lactis* factor (the same without glutamic acid), suggests that the human organism may be capable of utilizing a number of chemically similar compounds (with different microbiologic activities) in the synthesis of the erythrocyte maturation factor, or as the factor itself. This would account for the high antipernicious anemia potency despite low folic acid content (as measured by *L. casei* growth stimulation) of certain fractions.

Summary. 1. Seven patients with Addisonian pernicious anemia treated with folic acid are presented.

2. Adequate hematologic and clinical responses were obtained in each with doses varying from 2.5 to 30 mg. daily by mouth. The hematologic responses are shown graphically.

3. The minimal oral therapeutic dose for maximal response is 2.5 mg., or less, daily.

4. Combined sclerosis of the spinal cord is somewhat improved by folic acid therapy. The results are similar to those with liver.

5. It is suggested that the *L. casei* factor is either the antipernicious anemia factor or is utilized in its synthesis. Other compounds in liver with similar structures but without activity for *L. casei* may also be utilized by the human organism.

* The folic acid used in this study was supplied by Lederle Laboratories, Inc., through the courtesy of Dr. Stanton M. Hardy.

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RENAL FILTRATION RATES IN PREGNANCY TOXEMIA

INULIN AND EXOGENUS CREATININE

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ESTIMATES on rate of renal filtration, calculated from the excretory fate of injected inulin or mannitol,* depend upon a theoretically maximum no-threshold excretion of these sugars through kidney glomeruli, and upon an absence of their secretion or reabsorption in the tubules. According to Goldring *et al.*,¹¹ this figure amounts to 119 cc./min. plasma inulin in normal non-pregnant women. During uncomplicated pregnancy, filtration rates remain normal^{12,20,21} but are reported by some^{12,20} as slightly depressed and by others⁸ as raised in the early puerperium.

Investigators record a considerable variation of filtration rates in those patients with pregnancy toxemia.⁸ A tendency toward lower figures^{6,8,12,18,20} (compared with normal pregnancy) and a comparative improvement postpartum^{8,12,20} (contrasted with antenatal values) suggests interference with glomerular filtration. In most, the degree of antepartum suppression is commensurate with the severity of the disease.¹² Table 1 lists certain acceptable mean values for normally pregnant patients and for women with vascular syndromes, ante- and postpartum, and in subsequent follow-up.

Others^{8,20} divide patients with toxemia into 3 groups as to kidney function. The first includes those with diminished inulin and normal (or elevated) diodrast clearances,† the filtration fractions,‡ by consequences, being lowered. This group

belongs clinically to a preëclamptic type of pregnancy toxemia. Another includes those patients with normal inulin, decreased diodrast, elevated filtration fractions, and alleged evidence of essential hypertension. In a third group function tests are entirely normal. These observations are related to certain pathologic changes, a theoretically thickened glomerular basement membrane in the first group, and spasm, or organic change, in efferent renal vessels of the second. In the third group, that associated with normal function, the vascular status is considered relatively benign.

More recent studies^{3,7,15} on eclampsia and severe preëclampsia record a comparative antepartum suppression of uric acid clearance. This reduction, observed during short and prolonged clearance intervals,^{3,17} may relate to the blood elevation of this fraction in severe cases. Moreover, a mechanical interference with normal filtration, from a thickening of the glomerular basement membrane, might explain this increase in blood uric acid, although alterations in its tubular reabsorption occur in some severe toxemias. Bonsnes and Stander³ have observed a few cases with a normal urea but suppressed uric acid clearance. The accompanying elevation of blood uric acid without retention of other metabolites is puzzling. Difference in rate of tubular reabsorption or secretion, instead of selec-

* Inulin and mannitol are non-metabolized polysaccharides of high molecular weight. The filtration rate is obtained from quantity of inulin or mannitol excreted per minute (UV) divided by their plasma concentrations (P). Filtration rate (C_i) = UV/P .

† Mammalian kidneys excrete injected diodrast or para-amino hippuric acid by tubules and glomerulus. Because these dyes are removed from arterial blood in a single renal circulation (rapidly excreted, largely by tubules) their clearances express renal blood flow at low plasma concentrations and tubular mass (TM) at high. The formula, $C_i = UV/P$, affords either calculation.

‡ The filtration fraction (FF), the apparent fraction of plasma cleared through glomeruli, is given directly by inulin/diodrast ratio.

tive rejection by a supposedly inert membrane, the glomerulus, would best explain this observation; providing, of course, the modern and accepted theory of renal function is correct.

The following data, previously reported in part,⁷ and representing experience with simultaneous inulin, exogenous creatinine and urea clearance tests, are compared with contemporary results.

urea clearance determinations were obtained simultaneously from 15 patients. These results are tabulated (Tables 2 and 3). Patients were classified as to type of toxemia according to usual prerequisites, the final diagnosis being established in a subsequent 7 year follow-up.

1. URINARY OUTPUT. Employing a modified water diuresis test Dieckmann⁷ observed a reduced antepartum urinary

TABLE 1.—GLOMERULAR FILTRATION RATES—MEAN INULIN CLEARANCE VALUES
Expressed Cc./Min. Plasma (Adapted 3, 4)

	Normal pregnancy		Toxemia (cure*)		Toxemia (hypertension)		Follow-up toxemia ½ to 12 yrs. (3)
	(3)	(4)	(3)	(4)	(3)	(4)	
Antepartum . .	124	116	108	84	91	87	
Postpartum . .	116	139	120	105	110	95	94 3

* Taylor and co-authors²⁰ differentiate those patients followed by clinical cure from that group with subsequent hypertension.

Material and Method. Twelve pregnant women with vascular syndromes, 8 with signs of preëclampsia and 4 with hypertension, were selected for study. Of these, 5 were investigated ante- and postpartum. Additional studies were performed upon 2 normally pregnant patients, and upon 1 non-pregnant hypertensive woman.

Commencing at 0600,* after a previous midnight fast, the patient drank 200 cc. of water every ½ hour until completion of test. Breakfast consisting of 1 slice of unbuttered toast, and 200 cc. of milk instead of water, was consumed at 0730.* At 0800§ 10 gm. (100 cc.) U. S. Standard inulin was injected at the rate of 10 cc. (1 gm.) per minute, followed ½ hour later by 5 gm. creatinine by mouth. The clearance period, lasting 1 hour, commenced promptly at 0900.*

Blood specimens were obtained prior to 0800* for blanks and at exact mid-clearance period. Urine specimens were collected prior to 0800* for blanks and subsequently by catheter. Inulin analyses were as described by Alving *et al.*,^{1,13} the Folin methods being used for exogenous creatinine and urea. The formula, $C_m = UV/B$, calculated inulin and exogenous creatinine clearances, whereas the usual 2 formulas of Van Slyke were used for urea. Clearance values were corrected to a surface area of 1.73 sq. m.

Results and Discussion. A total of 46 inulin, 26 exogenous creatinine, and 41

flow, expressed as % of intake, in patients with toxemia. In this series experimental conditions necessitated a controlled intake ante- and postpartum. Resultant figures, computed as % increase in output postpartum, are quite labile (551 % mean average for 5 patients, or 371 % for 12 patients with toxemia), but suggest an improvement in urinary flow following delivery. In general, ante- and postpartum urine volumes paralleled corresponding clearance figures for inulin and exogenous creatinine. It would appear that low renal outputs were directly concerned with the number and permeability of active glomeruli and a maximum constant rate of water reabsorption in tubules.

2. UREA CLEARANCE. According to established standards⁷ the average values for preëclampsia and hypertension, ante- and postpartum, are 55 and 79 % for specific toxemias (former) and 64 and 76 % for the latter; whereas figures for normal pregnancy are 102 and 125 %. In Table 3 results are converted to % normal; these agree quite well with above standards, 56 to 92 % for preëclampsia and 81 and 77 % for hypertension. In general, urea clearance values paralleled those of inulin and exogenous creatinine.

* Military time.

3. EXOGENOUS CREATININE CLEARANCE. Although clearance rates for endogenous creatinine approximate those for inulin or manitol,^{14,19} it is contended that the former

is excreted partly by tubules, particularly in subjects with depressed renal function.¹⁴ Certainly the oral ingestion of creatinine materially raises its clearance.¹⁴ This

TABLE 2.—GLOMERULAR FILTRATION RATE—INULIN, CREATININE AND UREA

No.	Diagnosis	Ante- or postpartum	Urine (cc./min.)	Plasma clearance (cc./min.)		Urea clearance rate
				Inulin	Exogenous creatinine	
1	Hypertension	Ante	0.53	99	76	42.0
			1.13	86	..	32.5
		Post	5.53	141	179	74.0
			2.05	114	151	46.0
			7.00	159	..	67.0
2	Preëclampsia	Ante	1.60	130	..	17.0
		Post	3.66	233	..	96.0
			3.66	206	..	77.0
3	Preëclampsia	Ante	0.83	91	..	35.5
			0.46	74	..	35.0
		Post	3.46	118	98	64.0
			2.50	122	185	35.0
4	Hypertension	Post	2.90	88	68	55.0
			2.30	128	..	47.0
5	Preëclampsia	Ante	1.25	108	123	64.0
		Post	9.55	250	195	150.0
			8.20	219	275	121.0
6	Preëclampsia	Post	9.70	139	207	67.0
			7.10	148	201	63.0
			6.05	124	191	60.0
7	Preëclampsia	Ante	0.37	62	..	15.0
			1.07	46	137	25.0
			0.60	50	99	28.0
			0.93	64	132	29.0
			0.80	40	155	33.0
		Post	8.30	212	222	77.0
			7.50	111	191	55.0
			6.50	136	171	54.0
8	Hypertension	Ante	3.60	176	277	82.0
9	Preëclampsia	Post	6.50	105	..	53.0
			5.00	138	..	66.0
			3.80	165	..	57.0
10	Preëclampsia	Ante	2.93	138	219	67.0
11	Preëclampsia	Ante	1.63	67	..	20.0
			2.33	121	..	35.0
			2.37	102	..	34.0
12	Normal preg.	Ante	4.00	107		
			3.00	90		
13	Normal preg.	Ante	1.98	127	94	40.5
			1.26	130	115	44.0
14	Hypertension	N*	5.25	182	286	100.0
			3.80	133	215	67.0
			0.90	135	178	45.0
15	Hypertension	Post	1.10	135	..	30.0
			2.23	129	..	51.0
			5.90	134	..	48.0

* Not pregnant.

latter observation, interpreted as definite evidence of its tubular excretion, invalidates use of an exogenous method for measurement of filtration rates. In this series the exogenous creatinine clearance rate usually exceeded that for inulin.

4. INULIN CLEARANCE. According to Dill and associates,⁸ filtration rates for normal pregnancy are 116.14 ± 17.9 antepartum and 139.3 ± 16.1 postpartum. Thus, in this series, the mean inulin value antepartum was less than the lower limits of mean inulin deviation for normal pregnancy (Table 3). Antepartum values for preëclampsia are therefore comparatively low, improve markedly postpartum, and generally indicate interference with glomerular filtration in acute stages of the

improvement in postpartum filtration rates constitutes the chief phenomenon demonstrated by this method, although its cause, hormonal or mechanical or otherwise, remains in doubt.

Employing an azocarmine stain, Bell² describes a thickened glomerular capillary membrane in kidneys from eclamptic patients. The comparatively diminished filtration rates, observed in specific toxemias, have been assigned to this lesion which supposedly interferes mechanically with the normal filtration process.⁶ The consistent appearance of such a lesion in all cases of preëclampsia and eclampsia is questioned. Moreover, the rapid change from abnormal antepartum to normal postpartum filtration rates, covering so

TABLE 3.—GLOMERULAR FILTRATION RATE—COMPUTED AVERAGES

	Total		Plasma (cc./min.)		Urea mean % normal
			Inulin	Creatinine	
	Patients	Clearances	Mean	Mean	
Preëclampsia:					
Ante	6	13	84	144	56
Post	6	15	161	193	92
Hypertension:					
Ante	2	3	120	176	81
Post .	3	8	153	132	77
Normal pregnancy:					
Ante	2	4	96	104	
Hypertension:					
Non-pregnant	1	3	150	226	101

disease. In hypertension little change ante- and postpartum was manifest. A wide mean deviation occurred in toxemic patients. But, in general, these figures agree with those of previous reports (Table 1). Note, however, the tremendous diuresis manifested by some postpartum patients (Nos. 5, 6, 7 in Table 2). Urinary outputs of 540 to 600 cc./hour approach limits for maximum renal excretion. Glomerular filtration rates were high in some of these cases.

The low antepartum filtration rates, at least in specific toxemias, seems to be a consistent finding. But this reduction is scarcely sufficient to explain the markedly disturbed water and electrolyte balance present in such patients. The dramatic

little time as 96 hours in this series, makes anatomic changes unlikely.

Studies must be obtained from women with severe preëclampsia, during the acute phase, if these specialized methods are to be more completely evaluated. Most patients in this series had symptoms of severe toxemia. But all of these did not have suppressed inulin rates. One woman, No. 2, with muscular twitching, mental stupor, epigastric pain, hypertension, 4+ albuminuria and headache, had a normal inulin clearance, 130 cc./min. On the other hand, a second patient, No. 1, in whom toxemic symptoms were less severe, exhibited the most marked antepartum inulin suppression, 40 to 64 cc./min. (Table 2).

The appearance of oliguria or anuria during pregnancy toxemia constitutes a serious prognostic sign. With the advent of newer methods for kidney research it was hoped the mechanism of this suppression would become explained. Such was not the case. Most published data have been collected from patients with adequate urinary outputs; and it was impossible to measure clearances by the usual methods in women with anuria. This last difficulty could be obviated by injecting diodrast or p-amino hippuric acid, introducing a venous catheter (*via*. jugular to vena cava) to renal vein levels, collecting that blood and brachial arterial blood, and calculating renal blood flow. Such an extended procedure, however, is not always advisable. The following case report illustrates the difficulties encountered in investigating renal function in patients with anuria.

Case Report. CASE 1. A. S. (No. 6317), an unregistered 24 year old septagruvida, entered the hospital near term in coma with history of 3 convulsions. There had been a previous toxemia as well as hypertension during present gestation. In addition, a blood pressure of 230/160, 4+ albuminuria and normal fetal heart were noted. Usual therapy, consisting of hypertonic glucose, sedation and bag induction of labor, was followed by clinical improvement. However, 200 cc. sucrose was administered intravenously twice in the next several hours. Convulsions and coma reappeared. Anuria developed and the patient expired 24 hours after admission. Blood chemistry analyses disclosed depleted blood chlorides and acidosis. Arteriolar spasm was visualized during ophthalmoscopy. Microscopic examination of kidneys revealed marked swelling of nephron cells, avascular glomeruli and fatty degeneration of tubules.

This case, representing a patient with chronic vascular disease and eclampsia, was not subjected to the increased manipulations which a specialized renal investigation would have entailed. The risk was too great. Note that the intravenous administration of hypertonic glucose was

followed by some clinical improvement, but that injected 50% sucrose, injudiciously employed, terminated in anuria, convulsions and death. The depleted blood chlorides, 512 mg. per 100 cc. prior to injection and 244 mg. 4 hours later, contributed to the disturbed osmotic relationship. It serves to illustrate the advantage of intravenous hypertonic glucose which suppresses blood chlorides less and yet produces twice the osmotic effect of sucrose solutions. Large avascular glomeruli, typical for eclampsia, do not explain the presence of anuria. Urinary suppression is probably functional, not organic, in origin. Possibly the "fatty degeneration," observed in tubules of such cases, represents an effort at secretion rather than a degenerative process.

Probably the best opportunity to study renal suppression is found in toxic patients with complicating oliguria. Chesley⁴ has noted a suppressed endogenous creatinine clearance in oliguria induced by water restriction, and suggests that urine volumes vary with filtration rates. The results in this series, so far as low antepartum volumes are concerned, confirm that work, although the output was not artificially reduced, or below the level for oliguria, 0.5 cc./min. However, clearance tests conducted on patients with low urine volumes are notoriously inaccurate.^{5,19} It is often difficult to insure complete urine collection, and, at low outputs, the numerator of the clearance ratio (U/B) suffers disproportionate variations. Earle and Berliner¹⁰ propose a simplified procedure in which renal blood flow and glomerular filtration are measured simultaneously without the collection of urine specimens. A constant intravenous infusion pump delivers a measured amount of solution of known concentration. Since inulin (or mannitol) and diodrast (or p-amino hippuric acid) are eliminated almost entirely by the kidneys, clearance rates are calculated by dividing the amount of these chemicals injected per minute by their plasma concentrations. Such a method allows prolonged observation of

patients with oliguria and reduces errors usually ascribed to an inaccurate collection of urine specimens.

In the following case report, mannitol and p-amino hippuric acid were employed to measure filtration rate and renal blood flow.

CASE 2. P. K. (No. 375466), a registered 33 year old gravida 4, observed from the 12th week of pregnancy with hypertension, was induced near term, and delivered of a 2830 gm. living female infant. On the 8th postpartum day, a severe headache, dizziness, vomiting and blood pressure of 270/160 suddenly appeared. This was followed by a 6 hour period of oliguria, the hourly output being 10, 10, 65, 25, 10 and 20 cc. Mannitol and p-amino hippuric acid clearances were obtained. These were calculated as 53 cc. plasma/minute for mannitol, half normal value, and 650 cc. plasma/minute p-amino hippuric acid, an adequate figure for renal blood flow. During this hypertensive episode marked arteriolar spasm was detected in scleral vessels by capillary microscopy. Subsequently urinary function improved in this patient.

Transient oliguria has been produced experimentally by prolonged immersion of a limb in an ice-water bath.⁷ In addition, arteriolar constriction has been detected by ophthalmoscopy during an ice-water test.¹⁶ These observations suggest that

oliguria is due to a reduced rate of glomerular filtration. The angiospasm, observed in scleral vessels and representative of identical process in renal arterioles, may cause the urinary suppression observed in some patients with pregnancy toxemia.

Summary. Simultaneous inulin, exogenous creatinine, and urea clearance tests were obtained from 15 women, 12 of whom had severe signs of pregnancy toxemia. Urinary output, under identical conditions of fluid intake, improved markedly postpartum. Results for urea clearance compared favorably with established standards. With few exceptions figures for exogenous creatinine clearance exceeded those for inulin.

In severe preëclampsia, inulin, exogenous creatinine, and urea clearance rates were comparatively reduced antepartum, paralleled each other, and improved during the puerperium. Considerable variation in inulin clearance values exists in patients with pregnancy toxemia.

Severe cases, particularly those with oliguria, cannot be accurately investigated by the usual clearance methods employing collected urine specimens. Consequently, additional evidence is necessary to determine the exact mechanism of oliguria and anuria. The possible etiologic significance of angiospasm is postulated.

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PLASMA ANGIOTONASE CONCENTRATION IN NORMAL AND TOXEMIC PREGNANCIES*

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THE renal pressor system is the term commonly employed to describe the biochemical reactions mediating acute hypertension of renal origin. As illustrated in Figure 1, angiotonin (hypertensin) is formed by the proteolytic action of renin upon a protein which exists in small quantities in normal plasma, and is destroyed by an enzyme, or mixture of enzymes, called angiotonase (hypertensinase). Theoretically, hypertension could result from an increased concentration of either renin or renin substrate in the blood, or from a

various hypertensive disorders without finding any significant variations, but their series included only 1 pregnant subject.⁴

It is very likely that renin is present in small quantities in the plasma of all normal individuals,⁸ and it is quite possible, in fact, that the renal pressor system is one of the homeostatic mechanisms for the maintenance of normal blood pressure.⁷ If the angiotonase "deficiency theory"³ accounted for the hypertension of eclampsia, one should find a consistent lowering of plasma angiotonase activity

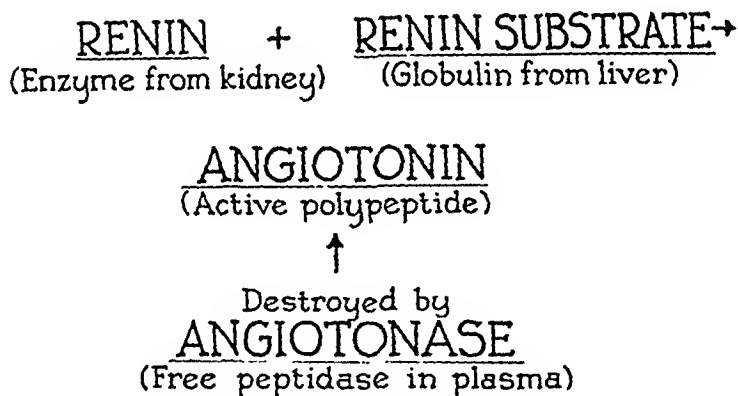


FIG. 1.—The renal pressor system

deficiency of angiotonase, and each of these possibilities has been suggested as a cause of experimental renal hypertension. The physiology of eclamptic hypertension has been discussed previously,¹⁰ and the work of Kellar and Sutherland⁵ supports the same thesis that the elevation of blood pressure in this disease is of humorally mediated chemical origin. Dexter and Haynes² demonstrated renin in the blood of 1 woman with eclampsia and in 2 out of 7 women with preëclampsia. They also studied the angiotonase levels of the plasma in human subjects with

in this disease. The present study consists of a quantitative estimation of plasma angiotonase in both normal and toxemic pregnant women.

Methods. Renin substrate was prepared from beef blood by adding an equal volume of cold saturated solution of ammonium sulfate to 2 liters of serum, dialyzing the precipitate for 18 hours in the cold and redissolving it in 1% saline in an amount equivalent to one-tenth the original volume of serum. Angiotonin was prepared by incubating 200 cc. of the substrate solution with 0.5 gm. of commercial (Smaco) hog

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renin for 15 minutes at 40° C., then lowering the pH to 5.5 and precipitating the proteins in a boiling water bath. The filtrate containing the angiotonin was stored at 6° C. under toluol.

A smooth muscle preparation most sensitive to angiotonin is the rat uterus.⁶ We found that the most satisfactory assays were obtained with the uterine horns of adult rats which have been ovariectomized about 2 weeks prior to use. This procedure abolished the spontaneous motility as well as the fluctuations of sensitivity due to the estrus cycle, but responsiveness of the uterus to angiotonin remained. In addition to its economy, the rat uterus method has the advantage of being insensitive to histamine, accurate to about the same degree as the blood pressure assay (plus or minus 20%), yet permitting multiple determinations on a small sample. The uterine horn is suspended in a 20 cc. capacity bath of Tyrode's solution maintained at 37° C. by a water jacket, and the writing lever is carefully counterbalanced for each strip. A stream of fine oxygen bubbles must come into contact with the uterus continuously. In matching responses, the mean rise of tonus, rather than the peak of the clonic response, is the more accurate indication of the dose. One "test dose" of angiotonin is the amount which produces an arbitrary 40 mm. response on the record (equivalent to an 8 mm. contraction of the uterine horn).

For the determination of plasma angiotonase, oxalated blood is collected with special precautions against hemolysis. Ten cc. of hemoglobin-free plasma is added to 40 cc. of 0.9% saline containing 50 "test doses" of angiotonin, adjusted if necessary to pH 7. An initial sample of 12 cc. is withdrawn immediately and inactivated with heat and acetic acid. The remainder of the mixture is incubated at 40° C., and 12 cc. samples are withdrawn at one-third less than the time estimated for half destruction, at the estimated half time, and at one-third more. (The time for destruction of half the angiotonin varies from 3 hours in a non-pregnant individual to about 30 minutes in a pregnant woman near term.) As each sample is removed, it is immediately inactivated and the filtrate is neutralized just before the assay. The percentage of angiotonin remaining in each sample may be plotted on the abscissa of semi-log paper,

with the time in minutes on the ordinate. A straight line is best fitted to the 4 points, the initial sample always representing 100% angiotonin concentration at 0 time. In this way, the time for 50% destruction may be easily found.

Our unit of angiotonase activity is that described by Plentl and Page¹² and is based upon the kinetics of a first order reaction. Angiotonase units (a.u.)/cc. of plasma =

$$\frac{0.693}{\frac{1}{2} \text{ time (min.)}} \times 100 \times \text{plasma dilution.}$$

In the method described, where the plasma dilution is always 1 in 5, a.u. at 40°/cc. =

$$\frac{346}{t \frac{1}{2} \text{ (min.)}}$$

RESULTS. The plasma angiotonase concentrations are illustrated in Figure 2. In 10 healthy non-pregnant subjects, there were from 0.9 to 2.5 units of enzyme activity/cc. of plasma, with a median value of 1.4. In the first half of pregnancy (5 cases), there was a moderate elevation, but this was not manifested during the first trimester. In the second half of pregnancy (11 cases), there was a progressive increase, the values ranging from 5.8 to 13.8, with a median value of 7.6 a.u./cc. Four samples of fetal cord blood showed the same concentration as the maternal blood (5.8 to 11 units). Plasma angiotonase falls to normal levels within a few days after delivery.

In 5 cases of preëclampsia, 3 gave normal values for the corresponding stage of pregnancy and 2 were low. Similarly, in 5 cases of eclampsia, 3 were normal and 2 were low. There was no correlation between the plasma concentration of angiotonase and either the severity of the disease or the level of blood pressure. The 2 most severe cases of eclampsia, for example, had the highest and the lowest values respectively, and the angiotonase concentration in the patient with the highest blood pressure (220/140) had a concentration of 10 a.u./cc. plasma.

Discussion. The cause of the 4 to 10-fold increase in plasma angiotonase in normal pregnancy is not known, nor is its physiologic significance clear. Other en-

zymes, such as histaminase¹ and pitocinase⁹ show a similar though much more marked increase during pregnancy, and it is possible that both of these, together with the enzymes which we refer to as angiotonase, are contributed directly to the maternal blood by the placenta. Curiously enough, there are marked variations in the plasma concentration of all 3 enzymes in the presence of preëclampsia or eclampsia, supporting the conclusion that the enzyme changes are not the cause of the hypertension but the reflection of a more general and profound biochemical disturbance associated, perhaps, with an alteration of placental function.

angiotonin. This was tested on a short series of 9 patients by Dr. L. A. Sapiststein in the following manner: A slow intravenous infusion of normal saline was started and the blood pressure recorded every minute until a basal level was established. The angiotonin (0.4 cc. of a sterile solution kindly supplied to us by Dr. O. M. Helmer of the Eli Lilly Co.) was then introduced into the venoclysis tubing in order to avoid both the pain and psychic stimuli associated with venipuncture. The diastolic pressor response was plotted and the rate of disappearance was determined by extrapolation to the original base line. On 4 non-pregnant gynecologic patients,

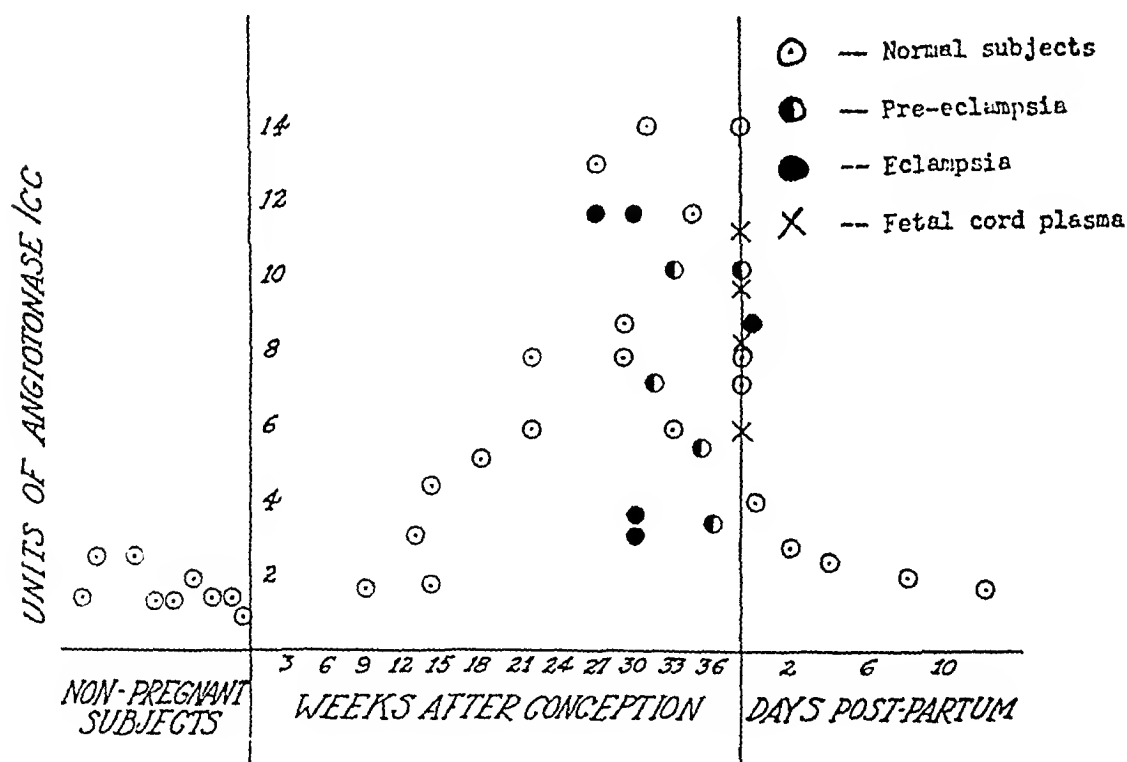


FIG. 2.—Plasma angiotonase concentrations during pregnancy

It was pointed out by Sapiststein, Reed and Page¹⁴ that the greatest part, if not all, of the destruction of angiotonin under physiologic circumstances occurs in the plasma. The duration of the pressor response to intravenously injected angiotonin varies inversely with the plasma angiotonase concentration. One might anticipate, therefore, that pregnant women should show a diminished response to

the average duration of blood pressure rise was $6\frac{1}{4}$ minutes (angiotonase level, 1.5 u./cc. plasma). On 2 puerperal women, 48 hours after delivery, the pressor response lasted $5\frac{1}{2}$ minutes (average angiotonase concentration at this time is 2.8 u./cc. plasma). On 3 puerperal women 24 hours after delivery, the pressor response lasted only $3\frac{1}{4}$ minutes (average angiotonase value, 4 u. at this time).

While we did not test any women before delivery because of the possible risks of oxytocic effects of angiotonin, we would anticipate from these data that the blood pressure response of a woman at term to the same dose would last for only 90 seconds. By analogy, pregnant women would be far more resistant to the blood pressure raising effects of renin, inasmuch as the latter depends upon the formation of angiotonin *in vivo*, and therefore pregnant women would be less susceptible to hypertension resulting from renal ischemia. If the angiotonase content of the plasma is similarly elevated in the plasma of pregnant rats, it would account for the resistance of pregnant animals to the effects of renal ischemia¹² as well as for the decline of renal hypertension during the latter part of a rat's gestation, a decline which we have shown to be dependent upon the presence of a placenta rather than the fetuses or the endocrine changes.¹¹

The fact that fetal cord plasma contains the same high levels of angiotonase as the maternal plasma suggests that this enzyme, unlike pitocinase, is able to traverse the fetal capillaries. We might anticipate that the enzyme would also be lost through the damaged glomerular capillaries in cases of eclampsia, along with other plasma proteins, and this would be the most likely explanation for the low plasma concentrations occasionally encountered in toxemic pregnancies with marked proteinuria. Unfortunately we have no data on the angiotonase activity of the urinary protein in these cases.

Summary. Assuming that the hypertension of eclampsia might be of renal

origin, the possibility exists that it is based upon a deficiency of plasma angiotonase (hypertensinase) activity, since the primary site of angiotonin destruction is the plasma. Accordingly, the plasma concentrations of angiotonase were measured in 10 healthy non-pregnant subjects, 16 women with normal pregnancies, 5 cases of preëclampsia and 5 cases of eclampsia. Observations were also made upon the fall of plasma angiotonase after delivery, the concentration of the enzyme in fetal cord plasma, and the correlation between the plasma angiotonase level and the duration of the blood pressure response to intravenously injected angiotonin.

It was found that there is a 4 to 10-fold increase in plasma angiotonase concentration in the second half of normal pregnancy and a rapid return to normal after delivery. The same high levels were noted in fetal cord plasma. Puerperal women with elevated angiotonase values were found to have a diminished pressor response to intravenously injected angiotonin; it would be anticipated, therefore, that pregnant women (like pregnant rats) would be more resistant to hypertension resulting from renal ischemia.

In the cases of preëclampsia or eclampsia, 4 out of 10 cases had values of plasma angiotonase activity which were low in comparison to normal pregnancy, but still above the non-pregnant level. There was, however, no correlation between the degree of hypertension and the plasma angiotonase. This finding makes it unlikely that a deficiency of this "protective" enzyme or group of enzymes is the basis for eclamptic hypertension.

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DIAGNOSIS OF GENERALIZED AMYLOIDOSIS BY THE CONGO RED TEST: DEFINITIVE DIAGNOSTIC CRITERIA

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THE problem of the diagnosis of amyloidosis has always been an important one in the management of certain chronic diseases, particularly tuberculosis. Widely recognized as a frequent complication in this disease, recent studies have shown it to be even more common than suspected. Auerbach and Stemmermann,² in a review of over 2000 consecutive autopsies at Sea View Hospital, show that it occurred in over 22% of cases coming to postmortem. Rosenblatt¹⁷ found an incidence of 24.4% in 451 consecutive tuberculosis cases. Other authors have reported similar figures.^{6,9,12} And even these statistics are probably underestimates, since they are based upon routine examinations without the regular use of special stains. If methyl violet stains were done in every autopsy, at least in the liver, spleen, kidney and adrenal, many more cases of minimal and moderate amyloidosis would be found. Be that as it may, tuberculosis is still one of our most common diseases and amyloidosis its most common complication.

Until the introduction of the Congo red test by Bennhold⁴ in 1923, clinical diagnosis of amyloidosis was difficult and uncertain. Hepatosplenomegaly was the principal criterion and its frequent absence meant that diagnosis could be ventured with confidence only in advanced cases. Biopsy was of limited use since it was employed principally in those cases where the liver and spleen were palpably enlarged and anatomic confirmation was necessary, being used in this manner by Josefson¹⁰ (spleen) and Waldenström²⁴ (liver). Therefore, the introduction of a simple biochemical diagnostic test was indeed a boon to the clinician.

The rationale of the test was based upon firm anatomic grounds. Bennhold showed

(and he has since been amply confirmed) that amyloid substance has a special affinity for Congo red and when this colloidal dye is injected into the blood stream, it is removed from the plasma by the amyloid, so that when the blood is examined 1 hour after injection, the dye is no longer present ("absorbed"). Where amyloid is not present, most of the dye remains in the blood stream and is there found 1 hour later. Bennhold described 4 cases in his original paper who had complete absorption of the dye in 1 hour and who on postmortem showed amyloidosis. Soon after his paper appeared, other workers reported similar complete absorption confirmed by postmortem.¹⁸

However, difficulties with the test were apparent even during the first studies made with it. The first difficulty was that the test could not detect small amounts of amyloid. Bennhold described a case which had only 22% absorption and yet on postmortem showed splenic amyloidosis. Similar experiences of other workers led them to propose modification of the Bennhold technique to avoid this difficulty. Bennhold had injected 10 cc. of a 1% aqueous solution of Congo red and then had estimated the amount of dye present in the blood 4 minutes after injection ("the standard"). He next determined the amount remaining after 1 hour, the difference between the 2 specimens showing the amount absorbed during the intervening period. Paunz¹⁵ used much smaller quantities of the dye in order to make the test more sensitive, and his technique has been employed by other workers, but his modifications, as well as similar variations,⁵ have never gained wide popularity and Bennhold's method is still the basis for most of our present-day techniques.

Since technical improvement in the test have not been able to rid it of its inherent ability to detect small amounts of amyloid, this has become an accepted and tolerated deficiency, and is known as a "false negative" result.

A more important, and much more confusing, difficulty with the test is the "false positive." Here, the test indicates the presence of amyloidosis which is not there on postmortem. This has discredited the test with a number of workers. Jacobi and Grayzel⁸ voiced this dissatisfaction in 1945 and state that because of this "The test must therefore be considered as of little moment in the absence of symptoms or signs of amyloidosis." However, this criticism of the test is a misdirected one. The trouble lies not with the test but with the interpretations with which it has been surrounded. This dates back to the original paper by Bennhold in which he states that absorption of over 40% is either amyloid or nephrosis and that absorption of over 60% is indicative of amyloidosis. But this statement was based on inadequate evidence which was not strengthened by those who uncritically accepted his criteria in the next decades. Auerbach and his co-workers have shown on the basis of extensive anatomic material that absorption of from 40 to 90% was found just as well in cases who did not have amyloid as in those who did.^{11,21} This question was recently thoroughly studied clinically and it was demonstrated that absorption of from 40 to 90% could under no circumstances be considered diagnostic of amyloid.¹⁹ If this had been established during the early days of the use of the Congo red test, the number of so-called "false positive" tests would be far fewer and the test would enjoy greater popularity. This is not to say that cases showing less than 90% absorption may not have amyloid—such cases occur, but the test does not separate them from those who have no amyloid and who have the same percentage absorption. The test, in this absorption range, has no diagnostic

value and we should not call upon it for aid which it cannot give.

Despite those cases of amyloidosis with incomplete absorption, in whom the Congo red test does not help us in diagnosis, the test is still of very great value. This is recognized by the wide acceptance of complete, or practically complete, absorption as diagnostic for amyloidosis. Schönberger and Rosenblatt,¹⁸ 2 years after Bennhold's paper appeared, reported 3 cases which showed complete absorption of the dye; amyloidosis was confirmed at postmortem. Nathan,¹⁴ although using smaller quantities of the dye, accepted as positive only those tests in which no dye is present in the 1 hour specimen. Moschkowitz¹³ states that 100% absorption is reliable, and Cohen,⁶ on the basis of his clinical experience, states that complete absorption is diagnostic of amyloidosis. Vivoli²³ accepted as proof of the presence of amyloidosis the removal of the dye from the plasma *en totalité* while Pearlman¹⁶ considers absorption of over 90% of the dye as positive. Harmon and Kernwein⁷ state their position, "If a positive result, by which we mean complete removal . . . is obtained, there is little likelihood that the condition is other than amyloid disease. Only 1 case¹¹ of a 'false positive' is on record if the criterion just mentioned is accepted." Finally, the work of these observers was reviewed, and their own extensive material was summarized, by Stemmermann and Auerbach²¹ in 1944 who state that "90 or 100% absorption of Congo red dye is to be considered a positive result."

Nevertheless, despite these assurances, exceptions have been shown even to the rule that complete or almost complete absorption means the presence of amyloid substance in the body. This was first noted by Lipstein and Auerbach¹¹ in 1937 when they described 1 case of 100% absorption and 2 cases of 90 to 99% absorption which, on postmortem, showed no amyloid. Thirteen additional such cases were later reported by Stemmermann

and Auerbach,²¹ this number representing 6.5% of Congo red tests done upon 200 patients in whom autopsy showed no amyloid present. Thus, it would seem that a false positive test is not an uncommon occurrence even when comparatively rigid criteria are used.

Recently, an extended clinical study was undertaken to see whether any criteria could be established which would avoid even the infrequent errors noted above. As a basis there was taken the widely accepted approval of 90 to 100% absorption as a positive test. A further lead was noted in Stemmermann and Auerbach's observation²¹ that false positive tests, upon repetition, became negative.

Material and Methods. Sixty-one patients from the large patient population of Sea View Hospital were chosen for this study. Each case suffered from either pulmonary or osseous tuberculosis and had shown from 90 to 100% absorption on the Congo red test—this was the only criterion for inclusion in the group to be studied. Each patient was then thoroughly reviewed clinically, complete physical examination done, and serial Roentgenograms and clinical course reviewed to establish the duration and course of the disease. Laboratory studies included multiple urine examinations for proteinuria, casts, red cells and specific gravity, with other tests done where necessary. From the above the clinical diagnosis of amyloidosis was attempted.

Each case was then retested with the Congo red test. The technique used was Taran's²² modification of Bennhold's method, which has been adopted as standard by the Committee on Standard Laboratory Procedure of the American Trudeau Society.¹ This modification has been shown to result in fewer false negatives since colorimetric difficulties due to hemolysis are avoided.

Anatomic correlations were attempted in as many cases as possible, including those coming to postmortem and by biopsy in a much larger number. Biopsy was done of the liver or spleen in a few cases and of the gingiva in many others. The latter site has been shown to contain amyloid deposits in many cases of amyloidosis, although not in every case.²³

RESULTS. Our studies confirm the general proposition that complete or nearly complete absorption of Congo red can be used to establish the diagnosis of generalized amyloidosis. However, as will be noted below, several important conditions must be attached to this statement.

Tests Showing 90 to 99% Absorption. First of all, we have found that, contrary to previous statements, the absorption of from 90 to 99% of Congo red cannot be accepted as a reliable indication of the presence of amyloidosis. We studied 10 patients who showed 90 to 99% absorption. Upon retesting, 3 again showed 90 to 99%, while 7 on retesting showed less than 90% absorption. These figures are not as interesting or as informative as are the detailed analyses of the cases involved (see Table 1). Each of the 3 who showed no change on retesting had clinical evidence of amyloidosis; in addition, 1 had a positive gingival biopsy and another showed amyloidosis on autopsy. Of the 7 cases who had less than 90% on retest, 2 had clinical evidence of amyloid and each was proven morphologically, one by liver biopsy and the other by autopsy. The remaining 5 patients, however, showed no evidence of amyloidosis. Brief case reports follow:

CASE 2. G. T. This patient is a 52 year old white male whose pulmonary tuberculosis began in 1936, but has remained essentially non-progressive since that time and the patient is able to work at a part-time job. At no time has his liver or spleen been palpable and 27 examinations of his urine revealed a faint trace of protein 4 times. A routine test on Oct. 5, 1943, showed 90% absorption. The patient was retested on Feb. 4, 1946, but now showed 25% absorption. There is no explanation for this discrepancy.

CASE 3. C. C. This patient is a 25-year old white female whose disease began in 1938. She was admitted to Sea View Hospital in 1939. A right pneumothorax controlled her disease on that side and a left thoracoplasty was performed in 1942, but her sputum continued alternately positive and negative. However, her clinical

TABLE 1.—DIAGNOSTIC STUDY OF 10 PATIENTS SHOWING 90 TO 99% ABSORPTION ON CONGO RED TEST

Case	Previous Congo red absorption (%)	Duration of disease (yrs)	Course of disease	Clinical examination				Clinical diagnosis	Results of retest with Congo red (%)	Comment
				Liver	Spleen	Edema	Protein-uria			
1. R. B.	97	1	Quiesc.	1+	1+	2+	1+	Amyloid	85, 100	Gingival biopsy and autopsy both showed amyloid
2. G. T.	90	10	Quiesc.	0	0	0	0	Non-amyloid	25	
3. C. C.	90	7	Quiesc.	0	0	0	Occas.	Non-amyloid	50	
4. A. K.	94	6	Progr.	1+	0	0	2+	Amyloid	90, 100	Gingival biopsy positive for amyloid
5. J. L.	93	5	Progr.	2+	0	3+	1+	Amyloid	59, 64	Gingival biopsy and liver biopsy both showed amyloid
6. F. M.	90	9	Progr.	0	0	0	0	Non-amyloid	23	
7. H. P.	98	1	Quiesc.	1+	0	0	0	Non-amyloid	37	
8. R. L.	94	2	Progr.	0	0	0	1+	?	90	Gingival biopsy negative
9. O. D.	94	5	Progr.	2+	1+	3+	4+	Amyloid	90	Gingival biopsy and autopsy both showed amyloid
10. L. D.	95	2	Progr.	0	0	0	Occas.	Non-amyloid	29	Autopsy revealed no amyloid

TABLE 2.—SUMMARY OF DIAGNOSTIC STUDY OF 33 PATIENTS SHOWING 100% ABSORPTION ON CONGO RED TEST

Case	Previous Congo red absorption (%)	Result on retest	Comment
1 14	100	100	Gingival biopsy in each of these cases showed amyloid; autopsy was performed on 2 of these cases and in both showed amyloid
19	100	100	Gingival biopsy was negative; however, autopsy later showed amyloid
20 30	100	100	No biopsy was attempted in these cases
31	100	95	No biopsy was attempted; amyloid was present on postmortem
32	100	64	No clinical evidence of amyloid; see text
33	100	>0, 29, 50	No clinical evidence of amyloid; see text

condition remained good and she was discharged in April 1946 for follow-up care. At no time during her hospitalization was there any clinical evidence of amyloidosis. Liver and spleen were not palpable and, except for occasional faint traces, her urine showed no proteinuria. On May 13, 1942, a Congo red test was routinely done and showed 60% absorption. Five months later another Congo red test showed 90% absorption. Retested once again on Nov. 10, 1945, she showed 50.4% absorption.

Summary. This patient never showed evidence of amyloidosis. There is no explanation available for the variation in the results of the Congo red test.

CASE 6. F. M. This patient was a 27 year old white male whose illness began in 1937. A right thoracoplasty was done in 1939 and was revised in 1942. However, this therapy did not control the disease which was gradually progressive and the patient died on May 6, 1946, of pulmonary insufficiency. Three Congo red tests were done routinely. On Oct. 19, 1938, there was 60% absorption. On Mar. 7, 1941, there was 70% and on Nov. 26, 1945, there was 90% absorption. During all this time, the liver and spleen were never palpable and on many dozen urine examinations proteinuria was never found except on 1 occasion in 1941 during a febrile postoperative period. The patient was retested on Mar. 7, 1946, and was found to have 23% absorption. There is no explanation for the previous 90% absorption.

CASE 7. H. P. This patient is a 40 year old colored male who was admitted to Sea View Hospital July 18, 1944, with a 2 year history of pulmonary tuberculosis. He stated that he habitually consumed large quantities of alcohol. His liver was slightly enlarged and firm on admission, but his spleen has never been palpable. Sixteen urine examinations were made—a very faint trace of albumin was present on 2 occasions. On August 13, 1945, a routine test was done preparatory to presentation to Surgical Conference and showed 98% absorption. This was repeated April 2, 1946, and then resulted in 37% absorption. There is no apparent explanation for this discrepancy.

CASE 10. I. D. This patient was a 20 year old colored male who was found to have pulmonary tuberculosis during draft board examination in July 1944. He showed

symptoms for the first time in March 1945 when caseopneumonic tuberculosis of the left lung was found. His disease ran an active course with spread to the right side and he died of a pulmonary hemorrhage on Mar. 6, 1946. At no time was his liver or spleen palpable. His urine shows occasional very faint traces of protein (during periods when his fever reached 105.8° F.). A Congo red test was done on Nov. 26, 1945, and showed 95% absorption. This was repeated on December 5 and only 29% absorption was found. Autopsy was performed and revealed caseopneumonic tuberculosis, disseminated miliary tuberculosis, intestinal and laryngeal tuberculosis. No amyloidosis was found.

Thus, it will be seen from the above that only 3 patients out of 10 who had from 90 to 99% absorption remained within this range upon retesting. Two others, who showed decreased absorption on retest, were clinically and morphologically proven amyloid. One-half of the patients showed negative results on retest with no evidence of amyloid and 1 of these was proven non-amyloid at autopsy. We, therefore, feel that absorption within this range is not diagnostic of amyloid.

Tests Resulting in 100% Absorption. Thirty-three cases were available for study who had had 100% absorption in previously performed Congo red tests. Clinical evaluation and Congo red retesting of this group leads to the conclusion that 100% Congo red absorption is almost, but not quite, diagnostic of amyloidosis. Retest of the patients in this group showed that 30 of them remained 100% on the second test. Gingival biopsies confirmed the diagnosis of amyloidosis in 18 of 19 in whom it was attempted—and the 19th later came to postmortem and showed marked renal amyloidosis. In 2 other cases of this group in which autopsy was done, amyloid was found. In 1 case, retest showed 95% absorption; amyloid was present on postmortem (Table 2).

The 2 remaining cases, nevertheless, were disquieting, both showing negative results on retest. Summaries of their case histories are presented below.

CASE 1. F. DES. This patient was a 29 year old white female on admission to Sea View Hospital in April 1942, with a 6 year history of her disease. On admission, she was found to have pulmonary tuberculosis complicated by an empyema necessitatus. Thoracotomy, thoracoplasty and Seheide were done in 1943 and resulted in conversion of her sputum and control of her disease. After revision of her Seheide wound in 1945 she was discharged as arrested in January 1946. Clinically, no evidence of amyloidosis was ever present except for occasional traces of proteinuria. A Congo red test done on Feb. 7, 1944, showed 25% absorption. In July, a second test showed 100% absorption and 1 done on Dec. 17, 1945, showed 64% absorption. *The first test was done routinely before surgical conference, the second because of a palpable liver at the time of a biliary colic and the third in the course of this study.* There was no clinical evidence of amyloid at any time. The reason for the 100% absorption is unknown—any relation to the liver involvement is conjectural. At the time of discharge the patient had no evidence of amyloidosis.

CASE 2. M. C. This patient was a 24 year old white female on admission to Sea View Hospital in 1941 with a 2 year history of pulmonary tuberculosis. A left thoracoplasty was done in 1942, converting her sputum, and she was discharged as arrested in 1943. She was re-admitted in August 1944 with a giant cheek-valve cavity in her right lung. In March 1945 a right eavernostomy was done and her sputum has been negative since. At no time while under observation has she presented any evidence of amyloidosis clinically. Five Congo red tests were done in this patient, the first 4 routinely before presentation to surgical conference and the 5th during this study. The results are listed: Nov. 27, 1941, 60%; Dec. 23, 1941, 100%; Jan. 14, 1943, 80%; Mar. 12, 1945, 29%; Feb. 11, 1946, 50%. There is no reason to believe that the 100% absorption represented amyloidosis. There is no explanation for the variation of these results.

Our experience in finding that 2 of the 33 cases who had had 100% absorption showed negative results on retest is by no means unusual, as we have noted above.

This is quite in accord with the anatomic observations of Stemmermann and Auerbach²¹ who noted that in 200 consecutive autopsies which showed no amyloid in any of the organs and in which Congo red tests had been done during life, 9 had shown 100% absorption being truly "false positives." It seems clear that a single 100% Congo red absorption cannot be considered as absolutely diagnostic of amyloid. Our findings also support the observation made by Stemmermann and Auerbach²¹ that repetition of the test in patients with 100% Congo red absorption will tend to weed out cases without amyloidosis who might have shown, for some reason, complete absorption on their original test.

Tests Showing two Consecutive Complete or Nearly Complete Congo Red Absorptions. Since 90 to 99% absorption certainly shows no great diagnostic reliability and since even 100% absorption may occasionally be misleading, we have sought a possible definitive diagnostic criterion for the Congo red test. For this, we studied 21 patients who had shown, on 2 consecutive occasions, complete or nearly complete absorption of Congo red.

Our findings in this group were rewarding. Every patient who had shown a positive Congo red test on 2 occasions had a positive result upon retest (Table 3). Since this was in accord with our clinical and morphologic investigations of these patients, we have come to the conclusion that a definitive diagnostic criterion for the Congo red test may be established by requiring at least 2 complete or nearly complete absorptions before amyloidosis be definitely stated to be present.

These clinical impressions are in complete agreement with the autopsy experience at Sea View Hospital where there has never been a case seen which had 2 consecutive complete or nearly complete absorptions which did not have amyloid anatomically.²² Every case which has shown 2 such absorptions has always shown amyloid.

TABLE 3.—DIAGNOSTIC STUDY OF 21 PATIENTS SHOWING 2 CONSECUTIVE CONGO RED TESTS WITH COMPLETE OR NEARLY COMPLETE ABSORPTION									
Case	Previous Congo red absorption (%)	Duration of disease (yrs.)	Course of disease	Clinical examination				Clinical diagnosis	Result of Congo red retest (%)
				Liver	Spleen	Edema	Protein-uria		
1. A. R.	100, 100	15	Quiesc.	0	0	0	4+	Amyloidosis	100, 100
2. A. K.	98, 90	6	Progr.	1+	0	0	2+	Amyloidosis	95
3. R. E.	100, 100	7	Quiesc.	0	2+	0	2+	Amyloidosis	100, 100
4. M. K.	100, 100	4	Progr.	2+	0	1+	4+	Amyloidosis	100
5. J. P.	100, 100	25	Quiesc.	3+	1+	0	1+	Amyloidosis	95, 100
6. E. C.	100, 100	12	Progr.	1+	0	0	4+	Amyloidosis	100
7. H. H.	100, 100	15	Progr.	4+	1	0	4	Amyloidosis	100
8. H. K.	100, 100	7	Progr.	0	2+	0	1+	Amyloidosis	100, 100
9. E. K.	100, 100	15	Quiesc.	2+	0	0	4+	Amyloidosis	100
10. J. C.	100, 100	5	Progr.	2+	3+	0	4+	Amyloidosis	100
11. S. S.	100, 100	10	Progr.	4+	3+	0	1+	Amyloidosis	100
12. J. H.	100, 100	2	Progr.	3+	1+	0	3+	Amyloidosis	100
13. H. Y.	100, 100	3	Progr.	3+	1+	1+	4+	Amyloidosis	100
14. F. L.	100, 100	10	Quiesc.	1+	1+	0	2+	Amyloidosis	100
15. R. B.	100, 100	5	Progr.	4+	4+	0	1+	Amyloidosis	100, 98, 100
16. R. G.	100, 100	12	Progr.	0	0	0	4+	Amyloidosis	100, 100
17. P. O'D.	100, 100	5	Quiesc.	2+	1+	0	1+	Amyloidosis	100
18. L. C.	100, 100	5	Progr.	2+	0	0	4+	Amyloidosis	100
19. R. L.	98, 98	2	Progr.	0	0	0	1+	Amyloidosis	100
20. C. S.	100, 100	2	Progr.	3+	1+	0	1+	Amyloidosis	100
21. J. D.	100, 100	5	Progr.	3+	0	0	1+	Amyloidosis	100

Comment

Gingival biopsy: positive for amyloid

Gingival biopsy: positive for amyloid

Gingival biopsy: positive for amyloid

Gingival biopsy: positive for amyloid

Gingival biopsy: normal gingiva

Gingival biopsy: positive for amyloid

Biopsy of spleen; pos. for amyloid

Gingival biopsy: positive for amyloid

Gingival biopsy: positive for amyloid

Autopsy showed amyloid; gingival biopsy: normal gingiva

Gingival biopsy: positive for amyloid

Gingival biopsy: positive for amyloid

Gingival biopsy: normal gingiva

Gingival biopsy: normal gingiva

Discussion. There has now been accumulated sufficient clinical, experimental and anatomic data to assay reevaluation of the Bennhold Congo red test and to define adequate criteria for its use. First of all, there is little doubt that it is a valuable weapon in our diagnostic armamentarium. There are few diseases in which so simple and so useful a test is available. It is to be regretted that the test is still insufficiently employed in many institutions.

We propose the following criteria for the evaluation of the Congo red test. These are based on the morphologic data of Amerbach and his co-workers and upon the clinical studies reported here and elsewhere.

1. *Those Tests Showing From 0 to 89% Absorption.* These results must be considered as negative. Patients without amyloidosis almost always fall within this group. While it is true that their results are usually in the lower half of this range, they may be scattered anywhere within it. An analysis of 1000 consecutive Congo red tests at Sea View Hospital reveals that 86.8% of all tests are in this group (Table 4).

TABLE 4.—RESULTS OF 1000 CONSECUTIVE CONGO RED TESTS

% Congo red absorbed	No. tests	%	
0-9	64	6.4	
10-19	184	18.4	
20-29	202	20.2	
30-39	159	15.9	60.9
40-49	93	9.3	
50-59	64	6.4	
60-69	39	3.9	
70-79	30	3.0	
80-89	33	3.3	25.9
90-99	36	3.6	
100	96	9.6	13.2
	1000	100.0	100.0

Undoubtedly, there will be cases with amyloidosis which will show results within this range. In fact, out of 105 autopsied cases which showed amyloid, where the Congo red test had been done within 2 months of death, 24.3% showed absorption of less than 90%.²¹ Thus, false negatives will be present, but we know of no way

whereby the Congo red test, unaided by biopsy, can be used to differentiate them from cases without amyloidosis similarly falling within this absorption range. Nevertheless, these cases are not numerous and will not work too great a hardship on our diagnostic resources. They will occur, moreover, mainly in cases of minimal amyloidosis, which usually are of lesser clinical significance. This is an unavoidable deficiency of the test which must be put up with. Occasional false negatives must be expected if we are to avoid the greater embarrassment of the false positive.

2. *Cases Showing From 90 to 99% Absorption.* Patients who show this amount of absorption of injected Congo red often have amyloidosis. They have it more frequently than patients with, say, 50% absorption. But they frequently do not have amyloidosis, as has been seen from our studies above. Thus, unless clinical evidence of amyloid is present it would be unsafe to use the Congo red test with this amount of absorption as diagnostic evidence of amyloidosis. Therefore, absorption of from 90 to 99% is merely suggestive of amyloidosis (perhaps strongly suggestive when clinical evidence is present) but otherwise is of little aid.

3. *Tests Showing 100% Absorption of Congo Red.* A patient who shows complete absorption of Congo red 1 hour after the injection probably has amyloidosis whether or not clinical evidence is present. However, this is not always true. Occasional cases will occur when a 100% Congo red absorption will mislead us and will point to the diagnosis of amyloidosis when there is none present. We suggest that when 100% absorption is found a provisional diagnosis of amyloidosis be made but that it not be considered definitely established until the test be repeated and another complete or nearly complete absorption result.

4. *Tests Showing Complete or Nearly Complete Absorption on at Least 2 Occasions.* We believe that this rigid criterion should be established for the definitive

diagnosis of amyloidosis by the Congo red test: that a case not be considered amyloid unless 2 consecutive complete or nearly complete absorptions be obtained. We have never seen such a patient show a negative result on any further retest and no such patient has come to post-mortem without showing amyloidosis.

If the above criteria are adhered to, the Bennhold Congo red test will prove to be an exact instrument in the diagnosis of amyloidosis.

Summary. 1. The Congo red test is a valuable aid in the diagnosis of amyloidosis. It is based on the removal of intravenously injected Congo red from the blood stream by amyloid substance, if this be present.

2. Where only small deposits of amyloid substance are present, there will be failure to absorb appreciable amounts of Congo red. This will lead to a "false negative" result.

3. These patients, with small amounts of amyloid, show 0 to 89% absorption.

Patients without amyloidosis give similar results. The test does not differentiate between them, and in this range has no diagnostic value.

4. There is widespread acceptance of 90 to 100% absorption as diagnostic of generalized amyloidosis. However, it has been shown that cases occasionally occur which show 90 or 100% absorption and yet have no amyloid. These are "false positive" tests.

5. Clinical studies were undertaken to determine definitive criteria for the diagnosis of amyloidosis by the Congo red test which would avoid even the infrequent "false positive." The conclusion was reached that a patient should not be considered amyloid unless there is complete or nearly complete absorption on 2 consecutive Congo red tests. We have never seen such a patient show a negative result on further retest and no such patient has yet come to postmortem without showing amyloidosis.

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PROGRESS OF MEDICAL SCIENCE

PEDIATRICS

UNDER THE CHARGE OF

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SICKLE CELL ANEMIA

RECENT PROGRESS OF PEDIATRIC INTEREST

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BECAUSE of its high rate of occurrence in the American Negro—approximately 7% by most estimates^{5,9,14,26}—the sickle cell phenomenon has been subjected to hundreds of clinical and laboratory investigations. The variegated patterns of the disease picture have been portrayed comprehensively in the recent reports and reviews by Wintrobe,^{31b} Lewis,¹⁵ Mosely,¹⁶ Murphy and Shapiro,^{17a,b} and others. Agreement is universal that the disturbances exhibited by afflicted individuals can be attributed largely and probably entirely to some congenital and inherited defect of the red cell itself. The curious shapes in sickle cell anemia are expressions of the abnormality of the stroma. This survey summarizes some of the more recent advances in the deciphering of the biochemical mechanisms responsible for the sickling, and their relationships to the pathogenesis of symptoms and signs in childhood.

THE RED CELL. In 1939, Diggs and Bibb⁶ reported on what was then known concerning the red cell in sickle cell anemia, based on review of the literature and

personal observations of 47 patients with active sickle cell anemia at the John Gaston Hospital, Memphis, Tennessee. They pointed out that the structural alterations during sickling take place in a variety of ways, and that sickled cells take on a diversity of shapes and contours. Reticuloocytes do not sickle as readily nor as bizarrely as do the more mature cells. Normoblasts undergo changes in shape even less readily, though they too may sickle. The type of cell adjudged most characteristic is "the hyperchromatic elongated form, pointed at each end and curved in the middle. . . . There is no sharp line of demarcation between the round, the oval, the blunt elliptic, the elongated elliptic, the elongated with one end and with two points and the curved cells with double points." Target cells may also be seen. The elliptic and oat-shaped cells are deemed to have become irreparably changed in shape.

The red cells may exhibit striking anisochromia, with diffuse basophilia, Howell-Jolly bodies, etc. Price-Jones curves of 10 patients revealed marked anisocytosis,

with average diameter greater than normal. Nucleated rell cells are common. The reticulocyte count is elevated, the average for 42 patients being 15%. More detailed studies of mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration led Diggs and Bibb to concur with Wintrobe³¹ that the red cells in sickle cell anemia are usually of the normocytic normochromic type, with a tendency toward macrocytosis. In the fragility test bloods from patients with sickle cell anemia as well as sickle cell anemia displayed an increased resistance to hypotonic saline solutions. Some of the red cells of a few patients failed to break up even when suspended in distilled water. This increased resistance is ascribed to the ability of these cells to alter in shape without placing their membranes under sufficient tension to cause hemolysis.

The morphodynamics of the change in shape which takes place during sickling has been carefully observed by Ponder.²⁰ Those red cells which become sickle cells when the O_2 tension becomes reduced, he termed meniscocytes. In their usual discoid shape meniscocytes are indistinguishable from normal red cells and are referred to as premeniscocytes.

By pressing on the cover-slip in sealed wet preparations with a dissecting needle, Ponder was able, with the microscope, to observe meniscocytes in a variety of positions. Manipulation of position brought out a change in rigidity of the premeniscocytes before any recognizable change in shape. If a cell is turned up on edge, for example, the upper part tends to fall over in the middle like a sheet of paper, as if the cell were unable to sustain its own weight. A normal red cell, in contrast, has sufficient intrinsic rigidity to stand on end like a bit of cardboard. When currents in the fluid bring premeniscocytes into collision with one another one cell may bend almost at right angles in flowing over a rounded projection on another.

After the stage of change in rigidity comes the sickling phenomenon proper.

The rim of the cell becomes thicker on one side and thinner on the opposite. The thinning proceeds until continuity breaks down. The 2 newly formed ends then become separated by straightening out of the arc, which flattens the biconcavity between them as the degree of curvature decreases. The thinned and stretched material of the biconcavity then expands at its unsupported edge into a series of veil-like projections. As the arc continues to straighten the veil-like material of the biconcavity follows the change of form of the arc, and in the completed meniscocyte appears as a very thin and almost invisible fringe lying within the sickle. The entire process of meniscocyte formation takes place usually within 1 and 2 minutes. Measurements show that in sickling the average cell increases in mean thickness but the volume remains unchanged.

When oxygen is reintroduced these processes reverse themselves, resulting in a normal appearing cell shape without any sign of where the biconcavity had been except for a small refractile globule which may not persist for very long.

To account for these shape changes, Ponder hypothesizes that the hemoglobin in the cell exerts an "expansive force." This force is a function of the oxygen tension which, in the normal red cell, can produce only tension or turgor because the surface ultrastructure is intact but which, in the premeniscocyte and meniscocyte, produces sickling because the surface ultrastructure is defective.

The essential mechanism for the development of the expansive force seems related to the conversion of hemoglobin from the combined to the reduced state. In cells which have been lysed by water the residual cell bodies no longer alter in shape when the oxygen tension of the suspending medium is changed. In the normal red cell the forces of surface tension tend to induce a spherical form, whereas the intermolecular forces of the surface ultrastructure tend to maintain the biconcave disk shape. If the ultrastructure is weak, as is assumed to occur in the

protoniscoeyte, the form forces tend first to break, and then to distort, the C-shaped rim of the cell into the shapes which the meniscoeyte successively assumes. Conversely, diminution of the turgor-producing forces by oxygenation of the hemoglobin allows the intermolecular arrangements in the surface ultrastructure to re-establish themselves, and the disk form becomes restored, essentially by progressive re-curvedure of the C-shaped rim.

In 2 patients with sickle cell anemia Singer²³ observed a markedly increased resistance to lysolecithin. (Lysolecithin is a hemolytic substance contained in normal blood serum, which can be extracted and used as a means of testing red cell fragility.) A third patient, however, presented a normal lysolecithin fragility though the cells were saline resistant. Thus there was a lack of complete parallelism between the resistance of the red cells in sickle cell anemia towards hypotonic saline solutions and towards lysolecithin.

Studies on the blood of normal Negroes by Helm and Jacobs¹² revealed a high osmotic resistance of at least some of the red cells. In one woman with sickle cell anemia this peculiarity was greatly exaggerated.

Tomlinson and Jacob²⁸ concluded from experiments with washed red cells that carbonic anhydrase is probably present in normal active amounts in the red cells of persons with sickling, and that it does not enter into the phenomenon of sickling beyond the normal function of facilitating the exchange of carbon dioxide and oxygen. Sickling can be precipitated *in vivo* and experimentally by alterations in the ratio of combined to dissociated hemoglobin within the red cell.^{17b} In the presence of high oxygen tension most of the hemoglobin exists in the combined form as oxyhemoglobin, and the red cells tend to remain entirely normal in shape and behavior. As the oxygen tension is lowered and the contained hemoglobin becomes correspondingly dissociated to the reduced form, the red cells begin one by one to

sickle until finally (experimentally) 100% will assume some abnormal form. It would appear that each cell has a specific threshold for sickling determined by the percentage of reduced hemoglobin. When this threshold is reached sickling is abrupt and almost instantaneous.

Crassing the threshold in the opposite direction reverses the process. Sickled red cells when placed in contact with oxygen reassume immediately their original disk shapes and become indistinguishable from normal red cells.

Hann and Castle¹¹ have observed that red cells when stored *in vitro* increase progressively in volume, spheroidicity and fragility, and ultimately hemolyze. These progressive changes are believed to be caused by metabolic processes which increase the osmotically active constituents of the red cells. The authors suggest that stasis in the spleen and other organs may explain the hemolytic destruction of red cells which takes place in the active phase of this disease. The time required for samples of blood from patients with sickle cell anemia to run through an Ostwald viscosimeter was found to increase markedly when the oxygen tension of the blood was lowered to 40 mm. Hg or less. In contrast, serum or plasma from these patients, normal blood and blood from patients with other forms of hemolytic anemia exhibited no differences in the rate of flow in the viscosimeter, whether fully oxygenated or fully reduced. The suggestion made is that when any disturbance, such as an infection, leads to increased plasma viscosity or tendency to rouleau formation the resultant delay in the passage of red cells through capillaries decreases the oxygen content and initiates a vicious cycle of erythrostatics and of hemolysis.

A reëxamination of the behavior of the red cells in sickle cell disease has been made by Murphy and Shapiro^{17a} (1944). From the difference observed in the rate and extent of sickling between whole fresh blood and mediums such as serum and saline solution which contain no fibrin

meshwork, they revive the old hypothesis that sickling is in some way related to the development of the fibrin net. They confirm the accepted principle that the dissociation of oxyhemoglobin bears a direct relationship to the phenomenon of sickling, with the cautious reminder that sickling and the dissociation of oxyhemoglobin may be simply parallel incidents, causally unrelated. Indirect evidence, such as the resistance to sickling of immature red cells and the invariable reversible association between sickling and oxygen asphyxia of the cells, argues for a causal relationship between the two occurrences. The sickling threshold for red cells is somewhat variable, depending on age of the cells. The evidence indicates that as the cells age the threshold becomes lower. Some cells sickle when a small part of their hemoglobin is uncombined, whereas sickling in others may require dissociation of almost all of the oxyhemoglobin. No relationships were found to variations in electrolyte ionic balance, though the level of available potassium in the cell may be of some significance in the sickling phenomenon.

Prolonged administration of 80 to 100 % oxygen to patients with sickle cell anemia was undertaken by Reinhard, Moore, Pubach and Wade,²¹ to determine whether the oxygen tension of arterial blood could be raised sufficiently to decrease the extent of the intravascular sickling. It was hoped that this might reduce the rate of hemolysis, with consequent lessening of the degree of anemia and with relief of pain during sickle cell crises.

Pure oxygen was given without interruption for 8 to 20 days to patients having abdominal or muscular pain, with no relief being obtained. Within a short time after the flow of oxygen was started, nevertheless, the percentage of sickled cells in both venous and arterial blood decreased decisively in the venous circulation, often from over 40 % to less than 20 %. This change persisted as long as pure oxygen was breathed. The oxygen content of the arterial blood became increased so

that it equalled or exceeded the oxygen capacity. No consistent change occurred in urobilin excretion in urine or feces to indicate that the rate of hemolysis had been materially altered.

The most dramatic results of prolonged giving of oxygen were: (1) a fall in reticulocytes which usually began on the 4th to 6th day and which lowered the level from the initial 20 to 30 % to as low as 1 %, and (2) a fall in the red cell count, which usually began on the 6th to 8th days and was as great as 0.5 to 1.5 million red cells. The giving of nearly 100 % oxygen thus depressed erythropoiesis—the physiologic antithesis of the erythroid stimulation produced by low oxygen tensions. After the oxygen was discontinued the reticulocytes rose again, to reach a peak of occasionally more than 50 to 80 % on the 5th to 8th day, and the red cell levels began to increase coincidentally.

A critique of the methods commonly advocated for detection of the sickle cell trait has been presented by Diggs and Pettit.⁸ Of the methods tested, namely the moist preparation, the gas chamber method, the moist stasis preparation, the test tube method, and moist preparations plus dyes and other chemicals, the procedure which proved most reliable and practical was the moist stasis method. In this procedure a rubber band is placed around the proximal portion of the subject's finger and allowed to remain for 5 minutes before the finger-tip is punctured to obtain a drop of blood. The blood is sealed under a cover-slip, and left up to 24 hours before the final reading is made. It is always advisable to make several moist stasis preparations from each patient to guard against artefacts, and the preparations should be made rapidly to prevent insofar as possible the exposure of the drop of blood to the air. Nevada and Rosen¹⁸ claim that sickling in artificial circumstances can be accelerated by adding a droplet of a broth culture of normal feces to the blood placed on the testing slide.

Active vs. Latent. The active variety (known customarily as "sickle cell anemia" or "disease") is a chronic hemolytic disturbance associated with striking blood changes and obvious signs and symptoms. The latent variety, known as "sickleleminia" or the "sickle cell trait," is viewed as non-productive of symptoms and free from blood changes, apart from the tendency of a proportion of the red cells in wet preparations to assume the characteristically bizarre shapes.

It has been known for some time¹⁴ that the red cells from individuals with sickle cell anemia change shape more rapidly and in greater numbers than those from individuals with the sickle cell trait. Sherman²² discovered that a much lower atmospheric pressure, *i. e.*, a much lower oxygen tension, is required to produce sickling in the sickle cell trait than in sickle cell anemia. In wet preparations at pressures of approximately 50 mm. of mercury the sickling was regularly produced in the red cells from 4 patients with anemia but not at all in 3 patients with the sickle cell trait.

Sherman carried this observation to the *in vivo* situation. He filled the dead space in a Luer syringe with white oil, attached a needle and withdrew blood from patients in the usual manner. Without exposure to air about 1 cc. of the blood so obtained was injected into 2 or 3 cc. of saline formalin under oil, and examined microscopically after a few minutes allowed for fixation. Sixteen such tests on patients with sickle cell anemia showed in every instance between 30 and 60% of the red cells to be in characteristically sickled forms in the venous circulation. Eight similar tests on 6 patients with the sickle cell trait showed no sickle cells in the venous circulation in 4 instances, and only a rare sickle cell (less than 1%) in each of the remaining tests. Application of a tourniquet for 10 minutes before the test failed to show any marked effect in either class of patients. This method is presented as a quick and simple diagnostic test between

sickle cell anemia and the sickle cell trait. Interestingly, arterial puncture performed in this manner in sickle cell anemia revealed up to 20% of the red cells "incompletely sickled," whereas venous blood obtained at the same time from the same patients showed between 40 and 60% of the cells to be "more definitely sickled."

Sherman found also that in sealed standing preparations an increased leukocyte concentration, a temperature elevation, and bacterial contamination each accelerate sickling, whereas saline dilution and increased oxyhemoglobin concentration retard the phenomenon. "This furnishes an explanation of the inconsistency of results obtainable with this method."

SEDIMENTATION RATE. It is well known that there exists a definite association between the tendency of red cells to form rouleaux and their sedimentation rate. The rapidity of the sedimentation rate usually is inversely proportional to the rapidity of sickling. Bunting² noted that sickled red cells from patients with either sickle cell anemia or the sickle cell trait failed to form rouleaux or to sediment appreciably within 1 hour. Non-sickled cells from these same patients formed rouleaux and sedimented normally.

In 6 of 10 patients with sickle cell anemia studied by Winsor and Burch^{30b} the sedimentation rates were unusually slow. Experiments indicated that this delay was linked to the degree of carbon dioxide saturation of the blood. The retardation in rate of sickling was greater as the carbon dioxide content became raised, as after re-breathing, or on exposure of the red cells to carbon dioxide *in vitro*. Conversely, inhalation of pure oxygen by the patients, or exposure of the red cells to 100% oxygen *in vitro*, accelerated the rate. The fact that the sedimentation rates of the patients became accelerated by breathing 100% oxygen meant, to Winsor and Burch, that the blood of these patients was not fully saturated with oxygen when breathing air. This led to the recommendation that when operation is necessary for these patients

an anesthetic gas which does not produce anoxemia is to be preferred.

Winsor and Burch^{30b} ingeniously devised some simple tests, called the "diagnostic parameter," based upon the faculty of the sedimentation rate in sickle cell anemia to be increased by oxygen and decreased by carbon dioxide. These tests were found to be 98% reliable in the identification of sickle cell anemia. In the "aëration-tourniquet" test a tourniquet (blood pressure cuff) is applied to an arm for 6 minutes to produce venous stasis. Five cc. of blood are drawn from a vein and placed in a small vial containing an anticoagulant, stoppered, and rotated gently to avoid mixing the blood with air. A sample of the blood is set up for a sedimentation measurement immediately. The remainder of the blood is rotated in air in a small beaker or Erlenmeyer flask, to saturate it thoroughly. The sedimentation rate of this aërated blood is also determined. Within 15 to 60 minutes the difference between the rate of fall of the aërated and non-aërated samples should be greater than 20 mm. per hour if the patient has sickle cell anemia. As soon as this parameter is reached, the test need not be continued further. A similar but more difficult approach is to withdraw blood from the arm, expose half to oxygen and half to carbon dioxide in separate containers, and note the difference in rate of sedimentation.

PATHOGENESIS OF LESIONS. Changes in local organs can be attributed to the abnormal red cells, whose contours and rigidity interfere with smooth passage through narrow capillaries. As Murphy and Shapiro^{17a} express it, the red cell may be flexible and elastic in its disk form but the moment it sickles it becomes "fixed and rigid as a crystal of ice as it moves about and abuts against cells and fixed objects." The end-to-end length of the sickled form may range from 2 to 5 or more times the transverse dimension of the intact red cell, with long processes tapering from the ends. This distortion of shape and inflexibility give rise to a

tendency for the abnormally shaped cells to interlock and jam within the microscopic circulation. The capillaries, sinusoids and small blood-vessels dilate, and the flow becomes sluggish. The local anoxemia which follows leads to still further deformities in cellular shapes, and soon the fine arterioles become occluded and begin to thrombose. The end of the process is local ischemia and necrosis, particularly in areas with poor collateral circulation.

Thrombosis of blood-vessels appears to be the most constant pathologic finding in sickle cell disease. In the pathogenesis of infarcts the first step is not anemia but thrombosis. Though conditioned by local anatomy, the mechanism is much the same in all organs. Death is usually due to some complication related to circulatory stasis.

Red cells are more likely to be sickled in the venous than in the arterial system. In active cases sickled cells are also found in large numbers in the liver at autopsy^{1,7} and in the spleen at autopsy and at splenectomy.²⁵ In both of these organs the flow of blood can be slow, giving the red cells ample opportunity to discharge their oxygen.³² Murphy and Shapiro^{17b} believe that the fibrosis and hemosiderosis characteristic of the spleen in sickle cell disease may be secondary to the sickling and stasis which obtains in that organ. "The sickled cells and the stasis lead to thrombosis of vessels, with infarction and subsequent scarring and contraction."

Practically every organ of the body may be affected by the process, giving rise to a rich diversity of symptoms and signs.³⁰ The cardiovascular system is affected in about 90% of patients, according to Winsor and Burch,³⁰ who cite how a diagnosis of rheumatic or congenital heart disease was made erroneously in more than half the patients at one hospital. Lesions of the nervous system have produced paralytic changes thought to be poliomyelitis; pulmonary infarcts resemble bacterial or a typical pneumonia; involvement of the abdominal viscera,

spleen, liver or gastro-intestinal tract can mimic ruptured peptic ulcer, ruptured gall bladder or acute appendicitis, leading to surgical intervention and carrying a high mortality.

Stasney's²⁴ study of 12 spleens from patients with sickle cell disturbance revealed active erythrophagocytosis by the Küpffer cells of the liver, and occasionally also by the reticulum cells of the spleen. The changes in the spleen were chiefly those of abnormal distention of the perfollicular sinusoids, hemorrhage and hemosiderosis. There was a propensity for the spleen to be large in childhood, small and atrophic in adult life. A significant comment was that no salient distinctions could be found between the clinically active and clinically latent forms of sickle cell disease. The "inactive" cases exhibited the same sort of changes as the "active" ones, the differences being only in degree.

Autopsy sections from more than 150 spleens of patients with sickle cell disturbances were examined by Tomlinson.²⁷ No congenital abnormalities of the arterial capillary endings in the red pulp cords of the venous sinusoids, or of the pulp cords themselves were found. The histologic picture was that of chronic active hyperemia of the pulp cords, especially in the marginal zones. These were packed with lamellated sickled red cells which were believed, because of their shapes, to escape only with difficulty through the stomata of Mollier. The arterial capillary pressure accentuates the packing of the cells. Tomlinson proposed that the "pooling" and intense packing of the sickled forms in time leads to thrombosis, hemorrhage, and scarring with calcium and iron deposits, resulting eventually in a small fibrotic spleen.

The hemolytic manifestations of the disease can be interpreted as being due for the most part to the lysis and resolution of the multiple thrombi. To explain the precipitation of hemolytic crises, Murphy and Shapiro^{17a} postulate that sickled cells accumulate in the circulation between crises, due to an increasing tendency of

the red cells to sickle as they become older. "The concentration of the sickled form eventually becomes so high that, possibly owing to alterations in the coagulating mechanism of the blood, they suddenly precipitate out in a more or less simultaneous capillary blockage." Far greater proportions of sickled red blood cells are destroyed in a crisis than are those still normal in shape. Thus, afterwards, relatively few red cells in the sickled form remain in the circulation. During the intervals between crises hemolytic activity still goes on, the long brittle erythrocytes being broken up by the trauma of capillary passage; a small degree of capillary thrombosis may also take place continually, contributing to the sustained low-grade hemolysis. The trigger mechanism which sets off the massive precipitation of sickled erythrocyte and blockade of capillaries is presumed to be an altered state of blood coagulability. "With each thrombosis there are liberated into the circulation certain coagulating bodies (thrombin, thromboplastin) which further enhance thrombosis and accelerate the precipitation out of the circulation of sickled red cells. A self-perpetuating sickle cell crisis is thereby inaugurated which gains momentum until the major part of the sickled cells are destroyed and the blood is again rejuvenated by release into the circulation of immature normally shaped cells. The sudden liberation of coagulating bodies into the circulation accounts for thrombosis of larger blood-vessels also."

Hyperbilirubinemia as the result of the increased blood destruction can give rise to stones in the gall bladder, by much the same mechanism as leads to these concretions in other varieties of hemolytic anemia.¹³ An excess of bilirubin in the bile favors aseptic precipitation of pigment in the biliary tract. Once the nucleus of a gall stone is formed, secondary factors such as stasis and infection determine its ultimate chemical composition. In most reports the stones have been described as multiple, small, greenish black and soft,

PEDIATRICS

of the pigment type. Weems²⁹ described such stones in 4 patients with active sickle cell disease. Their ages ranged from 13 to 38 years. In 12 of 44 necropsy reports reviewed, gall stones were either found at autopsy or had been removed surgically during the course of the disease. All of these patients were in the 2nd decade or older. Cholelithiasis in a Negro should always incite investigation for sickle cell anemia.

Differentiation between rheumatic myocarditis and the cardiopathy in sickle cell anemia is not always easy in childhood. Halpern and Faber¹⁰ have discussed this problem recently. The differentiation depends on the failure of pain in the extremities to respond to salicylates, the finding of jaundice, lymphadenopathy, or an abnormal spleen, the demonstration of anemia, reticulocytosis and sickling of the red cells, a slow sedimentation rate, diffuse cardiac enlargement, a prolonged P-R interval, and the characteristic bone changes associated with sickle cell anemia. Rheumatic carditis appears to be extremely rare in patients with sickle cell anemia.

HABITUS. The physical characteristics of patients with sickle cell anemia is "often striking and at times characteristic," according to Winsor and Burch,³⁰ who studied 15 patients, of whom 7 were children. The changes were most marked among adults in whom sickle cell anemia had been active for many years and least marked among children and those whose disease had been manifest for only a short time. Both height and weight were less than normal. The trunk appeared short and the legs long. Occasionally the head was elongated (dolichocephaly) or tall (scaphocephaly). When the disease was severe the neck was short and the head heavy. The normal spinal curvatures were accentuated, producing marked kyphosis and lordosis. Shoulders and hips were narrow. The arms and hands were long and slender and frequently the fingers almost touched the knees as the patient stood erect. The feet were elongated to a lesser degree.

In general the patients appeared frail and lacked muscular development and subcutaneous tissue. In children the chest was sometimes deep, and the abdomen often protruded sharply and markedly at the xiphoid process. The arms and legs were thin and stood out in sharp contrast to the abdominal enlargement. No abnormal habitus was observed in patients with sickle cell anemia. The majority of adult patients showed some gonadal hypofunction. This "dyspanocytic habitus" was believed to be independent of direct genetic factors and due exclusively to the continuing influence upon body growth of the anemia, influenced also by the endocrine and circulatory changes.

RACE. Cardoza³ studied the distribution of the blood Types A, B, AB and C, and also M, N and MN, in patients with the sickle cell trait, and found no marked tendency for the individuals who exhibited sickling to be concentrated in any one blood group.

Ogden¹⁹ recently reviewed the reported cases of sickle cell anemia in the white race and added 9 examples of the sickling trait (2 having active sickle cell anemia) in 2 white families. Both mothers had the sickle cell trait; each had transferred the disease in active form to at least 1 child and the inactive form to all other children. In 1 of these families, of German stock, Negro ancestry was established. The other family was of Spanish nationality.

Examination of the racial history in all reported cases led Ogden to the conclusion that in not a single case was the descent traced far enough back to exclude beyond question a possible Negro ancestor. With the exception of 1 American family, whose ancestry was studied for but a few generations, all white persons with sickle cell anemia reported on up to the present time have been of Mediterranean origin (Greek, Italian, Sicilian and Spanish). The invasion of the Mediterranean area by Hannibal and later by the Moors, the slave trade, and the participation of Negro soldiers in European wars have all served to bring the Negro in contact with the white in the

Mediterranean area. Ogden concludes, dogmatically, from his examination of the evidence, that "presence of the sickling trait in a white person is a definite proof of admixture of Negro blood in the immediate or remote ancestry."

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GYNECOLOGY AND OBSTETRICS

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THE VAGINA

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ARTIFICIAL VAGINA. There can be no doubt that a young woman without a vagina can be an object of pity, especially if her other sexual organs are developed and she has a desire to be married. For many years gynecologists have devised operations to construct an artificial vagina. Many of these operations utilized a part of either the large or small bowel, necessarily involving some form of intestinal resection. The mortality of such operations was high enough to discourage their use although in some instances the need for a vagina was considered so urgent as to justify a risk to life. In recent years the trend has been away from operations of this type because fairly satisfactory results have been obtained by safer methods. Wharton¹⁶ has been interested in this subject since he first performed his simple operation 20 years ago. He states that, in general, 2 methods of construction of the vagina seem to have replaced the older more complicated procedures: (1) the technique first performed by him in 1926 and published in 1938; and (2) the simpler procedure described by Frank in 1938. The former procedure is based on the principle first used by the author, that the adult vaginal epithelium will proliferate and cover a dissected space, just as the embryonic vaginal epithelium proliferates and forms the vagina in the fetus. Using this principle, one merely dissects out the requisite space for the

vagina and keeps it open by a suitable vaginal form; in time the epithelium from the vestibule or introitus will spread upward and over the dissected space with normal vaginal epithelium. Frank's operation is based on the principle that, in some young women, a space can be made between the urethra and rectum by firm, daily pressure of a hard tube, without any surgical dissection or anesthetic. Satisfactory vaginas have been made in this simple manner. This is the oldest of all methods of constructing the vagina, for a description of it was published more than 100 years ago; and, probably 25 years ago, the late Dr. Howard A. Kelly remarked that he had seen a case in which the vagina had been made solely by the perseverance of the husband. In general, it is best to construct vaginas only in women who are going to use them. If the constructed vagina is not used, it will probably contract just as the natural vagina does. The best results have been obtained in young women who have been recently married or are about to be. The ultimate result is liable to be questionable in older women who have never developed normal sex life, for, with advancing years, the sexual activities of both the husband and wife are apt to be on the wane. The question arises whether one should construct the vagina in women who have no ovaries, or who have been deprived of ovarian function, or in male pseudoherma-

phrodites who have been brought up as females. The answer to these questions is found in the study of each individual patient. In young women who have no ovaries at all, a satisfactory vagina can be made and maintained if it is used often. Even in male pseudohermaphrodites Frank has successfully made vaginas which have not contracted. The chance of making and preserving a functioning vagina is distinctly less if ovarian function is absent or if the patient does not have normal sex life. In deciding whether a vaginal construction is likely to be successful in any given case, the psychic and sexual attitudes of the patient are to be considered. Many women with normal vaginas have unsatisfactory coitus and complain of dyspareunia because of nervous tension, hypersensitiveness, and sexual frigidity. If the patient with gynatresia also has these psychic and mental traits, the chance of success is distinctly decreased. The technique which he has used is as follows: A transverse incision is made across the vestibule, where the opening of the vagina should be. If there is a rudimentary vagina, the incision is made across its vertex. A plane of cleavage is almost invariably found and can be followed without difficulty. As a rule, the vaginal space can be separated in 5 or 10 minutes, largely by blunt dissection. Having prepared the desired space, the proper vaginal form is then placed in it. He has used balsa wood forms in most of his recent cases because it is light, easily cut to any shape, and so cheap that one can keep a dozen or more forms ready at all times. They can be given to the patient. Each form is covered with a rubber condom, and sterilized by soaking in bichloride of mercury solution and then alcohol. A set of these forms is ready for use when one starts the operation and the appropriate size can be used in each case. Thiersch grafts are sewed over the form by interrupted sutures of the finest catgut (0000). The form is then inserted into the dissected space, and the operation is over. The form is not disturbed for

3 weeks; by that time the grafts should have taken strongly, and most of the vaginal walls should be firmly covered by healthy skin. The use of grafts hastens the covering of the vaginal walls and decreases the formation of scar tissue, which may develop with slower epithelization. If the grafts do not take, they will slough out, and there is an excellent chance that the vagina may then be covered by the spreading epithelium from the vaginal orifice, if the forms are kept in long enough. An indwelling urethral catheter may be used or not, as one chooses. The vaginal orifice must be large enough to avoid compressing the urethra between the pubis and the form, otherwise the terminal external urethra may slough.

Regardless of the choice of material or technique of operation, unless one dissects out a large vaginal space, the result will probably be disappointing. One should see to it that the space is deep (11 to 13 cm.), wide, and that the vaginal orifice is big, admitting 3 fingers. During the months after operation, the walls tend to contract, and hence one must create a space larger than is really needed. After the vagina has been made and is covered by epithelium, it may get bigger and deeper with coitus; but this does not obviate the necessity of having an adequate space to begin with. Bleeding is not commonly encountered in dissecting out the vaginal space. If it is, it should be controlled completely, so that the grafts may lie on a dry surface. The points which are most liable to bleed are the lateral walls at the level of the broad ligaments. During the dissection, one can feel these structures like bands of thin ribbon. If they do not yield to blunt dissection, they must be cut. Otherwise they will constrict the vagina at that point and give the vagina an hour-glass shape. Also, since these areas are vascular and convey the vaginal branches of the uterine vessels, they will bleed unless they are properly handled. Such vascular areas should be ligated by transfixion. Serious hemorrhage has occurred after

GYNECOLOGY AND OBSTETRICS

operation from inadequate hemostasis in this region. During the dissection of the vaginal space, there is not much danger of injuring the rectum or bladder if the plane of cleavage is normal and if the patient has not had a similar dissection before. Between the bladder and rectum there is normally a well-defined plane of cleavage, which permits the operator to separate these organs largely by blunt dissection. This dissection can be usually carried up to the peritoneum of the cul-de-sac without any trouble at all. But if the patient has had a former dissection in the region, a previous unsuccessful attempt to construct a vagina, then this plane of cleavage is replaced by scar tissue, and the rectum and bladder are glued to each other by dense fibrous tissue. Every moment of dissection, in such a case is fraught with the danger of perforating the rectum or bladder; such dissections are always difficult, tedious and long. Injuries to the bladder and rectum are common under these circumstances. Rectal perforations are more annoying because they always introduce infection. In 1 instance, the contractions of the abdominal and perineal muscles forced the end of the vaginal form through the apex of the vagina into the rectum 5 weeks after the operation. This made a hole 4 or 5 cm. wide in the apex of the newly formed vagina and transformed what appeared to be a perfect result into a possible disaster. He closed the fistula loosely by 4 or 5 interrupted sutures of 0 chromic catgut, packed the vagina loosely with xeroform gauze, and kept a large tube in the rectum for 2 weeks. The fistula closed completely, and 1 year later the patient had a large vagina 7 cm. deep.

The experience in this type of work which has been reported by Brady³ is unusual in that 4 different methods, determined by pertinent circumstances, were utilized to construct vaginas in 4 women in whom that organ was congenitally absent. Other surgeons have described their results in these cases, but in most instances each surgeon has recommended only one

form of treatment which he has used on all the women under his care. His experience would indicate that several different methods can, if properly used, be equally effective.

The choice of methods should be based not only on the anatomic findings present, but also on the temperament, the marital status, the intelligence and coöperation of the woman one is treating. Before attempting to make a vagina a surgeon must be familiar with the normal dimensions of that organ. Most authorities stress the fact that the anterior wall is shorter than the posterior because the vagina is united to the uterus at an acute angle. The length of the anterior wall varies from 6 to 8 cm. while that of the posterior from 7 to 10 cm. What is perhaps more important than the measurements of the normal vagina is what length and circumference are necessary for the completion of the sex act satisfactorily both for the woman and her husband. This will, of course, vary to some extent with the husband, but it is certain that in many instances a vagina considerably shorter than the normal length permits satisfactory marital relations.

In Brady's first case, because of the repeated attacks of appendicitis, a celiotomy was performed. This gave him an opportunity to inspect the pelvic organs. The uterus was normal in contour, but only 2.5 cm. in length. The Fallopian tubes were rudimentary. The ovaries were normal, the right showing a moderately well-developed Graafian follicle. The appendix was removed, and the patient was then placed in the perineal position. A circular incision was made around the outer margin of the mucous membrane surrounding the perineal depression, following the line where the skin and mucous membrane meet. By blunt dissection, the tissue under the mucous membrane was spread apart. Then, in the same manner, the tissue laterally, anteriorly and posteriorly were all gradually stretched until finally there was a tunnel 7 cm. in length and of sufficient

diameter to admit 2 fingers. The small circular bit of mucous membrane which had originally covered the very immature vagina had been pushed further and further upward while this was being done, so that it finally rested on and covered the top of the newly made vagina. However, all the rest of this 7 cm. long tube was raw and covered with neither mucous membrane nor skin. Using a method similar to, but not exactly like the method described by Graves, and later by Davis and Cron, the following attempt was made to cover over these raw areas. The labia minora were dissected off from above downward in such a way as to leave pedicles large enough to furnish good circulation. The available mucous membrane in each flap was increased by splitting apart from below the surfaces of each labium minus, thus converting the large folds into flat surfaces. These flaps were then sewed deeply into the vagina with No. 0 chromic catgut. The raw areas left by dissecting away the labia minora were then covered by sewing together the adjacent skin surfaces with interrupted sutures of plain catgut. Care was taken, both in making these flaps and later in covering all the raw areas, not to injure in any way, or encroach too closely on, the clitoris. This patient was fortunate in having unusually long labia minora, for by using them, as just described, it was possible to cover over the entire lateral and most of the anterior and posterior walls of the newly constructed vagina. Usually all that can be done with the labia minora is to cover over the lower part of the lateral walls, as the small lips are seldom long enough to stretch beyond this, no matter how the pedicles are cut.

In the second case, an operation was refused. This refusal came not from the patient, but from the man to whom she had been engaged for many years, and later married. He would not consent to his fiancée being subjected to the risk of an operation no matter how slight the danger might be, so he decided to try Frank's method. The patient was given

a pyrex glass rod $\frac{5}{16}$ inch in diameter, and told to press with this rod on the perineum over an area midway between the urethra and anus. At first, pressure was directed mostly backward, so as to keep from injuring the urethra. The direction of the pressure was changed at the end of a few weeks to upward and backward, following the same axis that the normal vagina takes. This patient was very intelligent and conscientious. She worked with the pyrex tube for at least $\frac{1}{2}$ hour, 2 to 3 times a day. Progress was slow, but steady. At the end of 6 weeks, there was an opening which would admit the tip of the finger for a depth of 2 cm. When a little bleeding would occur, as it occasionally would as a result of trauma, the patient stopped treatments for 48 hours. Six weeks later, the patient was able to introduce the glass rod 4 cm. She was then given a pyrex tube $\frac{5}{8}$ inch in diameter. Three months later, or about 6 months after treatment was started, 3 fingers could be introduced into the vagina which was now 6 cm. long. One might ask why not use this method always; but Brady thinks it has marked limitations. This patient treated herself for 6 months, and the treatments were definitely painful. Only her conscientiousness in carrying them out made success possible. She was never able to wear any of the vaginal forms recommended by others. She tried them, but was unable to sleep with the form in place, and could not carry out her duties as a nurse while wearing one in the daytime. When a patient has a small vagina to start with—perhaps measuring 3 to 4 cm. in length—this method would seem to be the best. Then, too, as in this case, it is all that can be tried when an operation is refused. However, when there is no vagina, or only a dimple 1 cm. in depth, few women would continue these treatments long enough to make the method succeed, and, therefore, in many instances, an operation is preferable.

In the third case Brady tried the method of Wharton which we have previously described. He made his dissection up-

ward slowly until only about 1 cm. separated the top of the newly made vagina from the large mass which he had felt on rectal examination, and which up to that time he had thought to be the uterus. This dissection upward was carried out until a vagina 7 cm. in length had been made. At this point he thought it wiser to make a lower abdominal incision and actually see the condition in the pelvis before burrowing further upward from below. After making this incision, he was surprised to see that what he had thought was the uterus was the patient's only kidney. There was no renal tissue in either renal fossa. The pelvic kidney was one-half again the size of a normal kidney. In this case there were embryologic defects in both the generative and urologic system. It has been pointed out by several writers that when there is a defect in 1 of these 2 systems, one should be on guard for abnormalities in the other. In spite of this he mistook, at least temporarily, the patient's only kidney for an enlarged uterus. If he had not recognized while operating, that he was dealing with something very unusual and had continued his dissection upward from the vagina, there is considerable likelihood that one of the large renal vessels might have been torn, with very serious consequences. In the future, in every case of absence of the vagina he will take a routine intravenous pyelogram before operating.

In the fourth case an inverted U-shaped incision was made through the skin, beginning just below the urethra and extending backward, and slightly laterally, until the dorsal end of the incision terminated 2 cm. ventrally and laterally to the anus. This incision was then continued through the subcutaneous fat for about 1 cm. Then, beginning at the ventral border, the tissue was undercut from above downward, forming a flap whose pedicle was the tissue in front, and just lateral to the anus. After turning the flap backward, the fat and subcutaneous tissue under it were carefully separated and stretched by blunt dissection until

there was a cavity into which 2 fingers could be introduced for a distance of 8 cm. In carrying out this dissection, the operator took special care not to come too close to the urethra, bladder or rectum. A retention catheter had been introduced into the bladder, and a rectal tube into the anus before the operation was started and, by means of these, it was possible to tell just how closely the dissection approached the urinary and intestinal tracts. In this case, there was never any danger of the urethra or bladder being injured. However, as the dissection was carried upward, the rectum seemed to be getting nearer and nearer until only a small amount of tissue separated it from the cavity that was being formed. Because of this, the dissection upward was stopped when the cavity measured 8 cm. The steps remaining in the operation were those which would cover this cavity with epithelium and which would prevent its postoperative obliteration through contraction. The first step in accomplishing this was to carry the U-shaped flap of skin and subcutaneous fat which had been made by the original incision deep down into the cavity and sew it to the underlying tissue. No. 0 chromic catgut sutures were used for this fixation. The flap measured about 6 cm. in length. By extending the ends of the original incision practically to the anal margin, this flap might have been made 1 or 2 cm. longer. To cover the anterior and lateral walls of the vagina, the labia minora were dissected off from above downward in such a way as to leave pedicles sufficiently large to furnish good circulation. The available mucous membrane in each flap was increased by splitting apart from below the surfaces of each labium minus, thus converting the large folds into flat surfaces. These flaps were then sewed deep down into the vagina with zero chromic catgut. Care was taken, both in making these flaps and later in covering all the raw areas, not to injure in any way, or encroach too closely on the clitoris. The only raw area that remained was in the uppermost part

of the posterior wall. To cover this with epithelium a mid-thickness split-graft, measuring 11 by 5 cm., was cut from the right thigh. This graft was sewed over a Wharton "vaginaform" made of balsa wood, then introduced into the vagina in such a way that it was in close contact with the remaining uncovered area. A retention catheter was left in the bladder. The patient left the operating room in good condition. There had been very little loss of blood.

Somewhat similar to the technique which Brady used in his first case and yet differing in details is the method reported by Falls.⁸ The operation is extremely simple, devoid of dangers and gives satisfactory results in the cases in which it has been used. As a rule, in these patients, the external genitalia are fairly well formed, and in many there is a slight pouch or at least a dimple in the perineum to indicate the normal location of the vagina. A circular incision is made around the edges of this dimple, creating a disk about 2 to 3 cm. in diameter. The edges of this disk are undercut, leaving the center attached to the underlying tissue. The loose connective tissue between the bladder and rectum is separated by blunt dissection, and the disk of skin is pushed inward to form the vault of the new vagina. Skin flaps about 1 cm. wide are cut from the edges of the vulvar opening by making lateral cuts at 3 and 9 o'clock, the width of the flap, and extending the incision upward and downward for about 2 to 3 cm., making 2 ribbons attached to the side of the vulva at one end which can be swung into the cavity, and the free edge sewed to the edges of the disk, forming the vault of the new vagina. The same is done on the opposite side so that there are 4 strips of vulvar mucosa 1 cm. wide, each attached externally to the edge of the vulva and internally sewed to the disk forming the vaginal vault by catgut sutures. The raw surface of the flap comes in contact with the walls of the cavity formed to permit sinking the disk, and the blood

supply is established between the 2. The flaps also get a good blood supply through their attached pedicle. Epithelization occurs between these transplanted strips of mucosa, and in about 2 weeks a completely epithelized tube is formed. During healing, the pouch is packed with gauze daily, and a moderate amount of pressure is maintained. After healing is complete, the pouch will be found to be about 2 inches deep, and may be deepened by wearing a vaginal plug at night and making rather strong pressure on the disk or vaginal vault daily. The patient can be taught to do this herself.

A much better understanding of all these operations can be obtained by referring to the illustrations which accompany the original articles.

The most that is expected of any of these operations is the provision of an artificial vagina that will permit reasonably satisfactory sexual relations. Therefore, the case reported by Whittemore¹⁷ in which a pregnancy followed one of the operations is certainly interesting and extremely rare. The patient was a woman of 21 operated upon for congenital absence of the vagina, which was present in association with a unicornuate uterus and a congenital absence of left kidney and ureter, left tube, ovary, round ligament, broad ligament and uterosacral ligament. There was also an abdominal left ninth rib. Within a few weeks after operation for the construction of an artificial vagina she became pregnant and later was delivered by Cesarean section of a full-term living baby.

At operation a No. 22 metal sound (F.) was first introduced into the bladder and held in the median line. With the left forefinger in the rectum, a 2 inch transverse incision was made midway between the external urinary meatus and the anus. By blunt dissection with the finger, the bladder was carefully separated from the rectum, until the cervix was finally felt. Much bleeding was encountered in this stage of the procedure from the perirectal venous plexus. The artificial cavity thus

created was enlarged laterally on both sides until the cervix with its external os was visualized and until the cavity would admit to its full length a vaginal glass speculum 10 cm. long and 3.8 cm. in diameter. The cervix was then seized with tenaculum forceps and pulled downward more into the range of vision. At this stage a fistulous tract was seen extending from the upper left side of the portio to the urinary bladder. Four sutures of No. 1 chromic catgut were placed through the upper and lower quadrants of the cervix and left long. Four plastic flaps were next constructed to serve as a lining for the new vagina as follows: (a) Two flaps of mucous membrane were constructed by partially removing both labia minora beginning at the clitoris and dissecting them down to a point just above the orifices of Bartholin's glands, including a broad pedicle at the base of each flap. Each of these was broadened out into a butterfly shape by incising the raw surface in its long diameter. (b) Then a flap was dissected from the inner aspect of each thigh consisting of the entire thickness of skin and subcutaneous fat. The 4 flaps were sutured together over an old-fashioned glass vaginal speculum as a form, thus constructing a tube with an orifice at its apex to fit about the cervix after the method devised by Graves. The 4 sutures of No. 1 chromic catgut which had been placed at the 4 quadrants of the cervix were threaded on a curved needle and brought through each of the 4 flaps near its apex. When these sutures were about to be tied, the glass form was removed and the entire tube was inverted, forming a lining for the artificially constructed vagina which was then packed with gauze overlaid with rubber dam. The thigh wounds were noted as reddened as early as the 3rd day, and by the 7th these began to gape. The left thigh flap had come out of the vagina and was partly necrotic. On the next day both thigh flaps had come out of the vagina and there was an increase in the purulent discharge. The perineal wound

remained fairly clean and on the 11th day the edges were approximated with an adhesive bridge and the granulations sprayed with aristol powder. The labial flaps took well. On April 5, under ethylchloroform anesthesia, a secondary closure of the thigh wounds was carried out. Granulating areas on the inner aspect of each thigh were curetted, the skin undermined above and below, and the skin edges freshened. Approximation of the edges was accomplished with pulley sutures and by plain interrupted sutures of heavy silk. From his experience with this operation, Whittemore would in the future use only the labia minora to line the artificial vagina and not try to employ skin flaps from the thighs. During the following 6 months the patient came to the office at bi-weekly intervals for dilatation of the artificial vagina. Coitus with normal orgasm was reported to have occurred 5 days after discharge from the hospital. Menstruation began on May 25 and lasted 4 days with a good normal flow from the vagina. A definite menstrual period occurred on June 27, and a very slight flow on August 7 which lasted only 2 days. Morning vomiting occurred several times, and on September 19 the uterus was found to be definitely enlarged and lying to the right of the mid-line. From this point pregnancy progressed normally with occasional symptoms of slight incontinence. On March 10, rectal examination showed the cervix to be $1\frac{1}{2}$ fingers dilated, but the patient was advised to enter the hospital for Cesarean operation. She was admitted on March 18 just 1 year after the operation. The indications for an elective Cesarean operation were the rather rigid, narrow artificial vagina, with congenital absence of the perineal body. There was also the question of the strength of the uterine wall because of the supposed absence of left adnexa and ligaments. Cesarean section was carried out on March 19.

VAGINITIS. Of the various types of vaginitis which are encountered, the one which has received the most attention

has been that due to the gonococcus. While the gonococcus does not infect adult vaginal epithelium, but causes a vaginal discharge by infection of the cervix, for the purpose of this review the term vaginitis will be used to indicate an inflammation of the lower genital tract, associated with a purulent discharge containing gonococci. A few years ago, many pages would have been devoted to the relative values of the various sulfonamides in the treatment of this condition. The availability of penicillin has greatly modified present-day concepts. According to Mulholland,¹¹ as we survey the situation regarding the use of chemotherapy and antibiotic therapy, the picture changes from month to month. Even though we see this passing parade of facts and figures, they may not impress us markedly if we do not take time to really catalog them. For instance the treatment of gonorrhea has changed greatly in the past 2 years. In the period 1940 to 1945 the percentage of cures was nearly 100 and hope was expressed that gonorrhea would be completely eradicated by means of the sulfonamide drugs. As time goes by, it is noted the percentage of cases not responding to sulfonamides is progressively increasing.

In the study of large groups of cases of gonorrhea in the Army during the past war, there is no doubt sulfonamide resistance is becoming more and more common. *In vitro* experiments show that some strains are normally more resistant than others, some being completely unaffected by the drug. Some strains appear to be naturally resistant while others acquire resistance, perhaps as a result of sublethal doses. If we assume gonococci are either sulfonamide resistant or sulfonamide sensitive, it would follow that the more people treated with sulfonamides, the more likely the most sensitive strains will be killed off and the relatively resistant strains survive. As time goes on this presents a rather poor prospect for adequate control of the disease with this drug. It would follow that all the preva-

lent strains in a decade or so would be sulfonamide resistant. Penicillin is not without some reactions and discomfort that may or may not be due to impurities. It has been reported that certain lots of commercial penicillin produce severe pain on intramuscular injection. On repeated injections, sterile abscesses containing insoluble material with no antibacterial activity have been reported. With increase in potency in units per mg., there is a corresponding decrease in the pain produced. Of the 3 sites of injection (buttocks, triceps and deltoid), the least amount of pain results from injections into the buttocks. Reactions of the allergic or serum sickness type are being reported each month. There is great difficulty in determining the source responsible for the allergic reaction. Penicillin as presently employed is not a pure product. Until pure crystalline components constituting crude penicillin can be activated in sufficient quantities to permit their use therapeutically, incrimination of penicillin allergic responses must be held in abeyance.

The data compiled by the Public Health Service on the treatment of gonorrhea by penicillin have been reported by Heller,⁹ who states that the investigations were made by medical officers in charge of several hospitals established by state and Federal agencies for the intensive treatment of venereal disease. Two treatment schedules were studied: 1 that could be completed in 2 hours and another that required 3 hours. There were 396 patients studied, 248 white and 148 colored, 108 male and 288 female. In all patients the diagnosis was confirmed by a positive culture; 83 % of the patients were observed 10 days or longer, 17 % from 6 to 9 days. To be regarded as "cured" the patient had to be clinically and bacteriologically free of infection, *i. e.*, without signs or symptoms and with 3 or more cultures—all negative—during the observation period. The 2 hour schedule was administered to 255 patients. They received 200,000 units of sodium penicillin dissolved in 6 cc. of

water in 3 intramuscular injections; at zero hour, 50,000 units (1.5 cc.), at 1 hour 50,000 units (1.5 cc.) and at 2 hours 100,000 units (3 cc.). The 3 hour schedule administered to 141 patients called for the same total dosage administered intramuscularly as follows: at zero hour 40,000 units (1.3 cc.), at 1 hour 40,000 units (1.2 cc.), at 2 hours 40,000 units (1.2 cc.) and at 3 hours a final injection of 80,000 units (2.4 cc.). No patient showed evidence of toxic reaction, and although the injections were given at hourly intervals, the very short span of treatment was most acceptable both to the patients and to the medical and nursing personnel. Among the patients observed 10 days or longer, 94% were cured on the 2 hour schedule and 96% on the 3 hour schedule. Although there were no significant differences, the rate of cure on the 2 hour schedule was higher in the colored than in the white, higher in the female than in the male, and higher in the previously untreated than in the previously treated. In the small group of patients who apparently do not respond to treatment the diagnosis of gonorrhea may be in error, as shown in re-check of the organism on sugar fermentation mediums. Certain of the failure cases may require quite large amounts of penicillin given over a longer period of time and for this purpose may require hospitalization. But thus far research by the Public Health Service has not detected strains of gonococci which remain persistently resistant to penicillin.

According to Perkins and Brewster,¹² the application of penicillin seems to be the outstanding advance to date in the therapy of gonorrhea, the most frequent of all venereal infections. The results of treatment in both sexes, with or without complications, are so striking that all other forms of therapy now seem antiquated. There are enough failures of treatment to necessitate careful repeated follow-up examinations, which should include at least 4 or 5 cultures and smears for the gonococcus. The optimum treat-

ment schedule has yet to be worked out, but the underlying principles seem to aim at producing penicillin blood levels high enough to accomplish the desired results over a relatively short period rather than lower blood levels for a prolonged period. The rationale of this is twofold: the goal is to develop an ambulatory treatment that can be completed at 1 clinic session; and experience seems to show that dosage schedules that achieve these high penicillin blood levels produce a larger percentage of satisfactory results. Because of the well-known repressive action of the drug on the spirochetes of syphilis, blood serologic tests should be taken 6 weeks after treatment and should be repeated in 3 months. Two hundred and thirty-four courses of treatment were given to 200 patients with either proved or suspected gonorrhea. Those treated on suspicion without any particular clinical or laboratory evidence of gonorrhea were women who had been named as sources of infection by men with gonorrhea; in most cases these were military contacts. The largest group of patients in the series received 100,000 units of penicillin. In all but 6 of these patients, who were treated according to the schedule of 20,000 units every 2 hours for 5 injections, the results were satisfactory. Forty-one patients were treated with 150,000 units of penicillin. All of these were given 50,000 units every 2 hours for 3 doses. The results were 100% satisfactory. This schedule seemed to give the best results, which is surprising in view of the fact that the 44 cases treated with 200,000 units showed failures in 4, a rate of 9%.

The report of Cohn, Taylor and Grunstein⁵ is based on a series of 108 patients treated with penicillin. Of these, 101 had failed to respond to at least 2 courses of various sulfonamides; the remaining 7 patients showed a definite sensitivity to sulfonamide compounds. Of the total of 108 patients, 99 promptly became bacteriologically negative after 1 course of penicillin treatment, and 9 by the administration of a second course of penicillin.

The results obtained by the administration of various amounts of penicillin point to the fact that a minimum total dosage of 100,000 Oxford Units injected intramuscularly in divided doses, is both necessary and sufficient for bacteriologic cure. The minimum total period of time required for successful therapy was found to be 6 hours. Smaller doses of penicillin and shorter total time of treatment were adequate in individual cases, but this type of therapy cannot be recommended. After their discharge from the hospital, 81 of the total of 108 women were followed up for an average period of 43.6 days, during which an average of 3.5 examinations were performed. Fifteen patients were found gonococcus positive after an average follow-up of 51.7 days. It may be assumed for various reasons that all these patients represent reinfections rather than recurrences. No serious toxic symptoms appeared in this group of patients treated with penicillin.

An interesting study on the *vaginitis of childhood* has been made by Rice, Cohn, Steer and Adler¹⁵ and, although the work was done before penicillin became available, it is worthy of review at this time. It was arbitrarily agreed that children to be regarded as cured must be clinically normal and that at least 7 consecutive smears and cultures made during a period of at least 16 weeks must show no gonococci.

Forty-one children were observed who were not given any form of treatment. Some recovered within a short time, 54% by the 10th week and 87% by the 28th week after the beginning of observation. This is definite evidence that spontaneous cure of the disease may occur in the majority of patients. Thirty-three children were treated with estrogenic substances (amniotin and diethylstilbestrol). The 12 (36%) who were cured were treated for an average of 54½ days. Comparison with the control series showed that bacteriologically cure was no more frequent among patients given this form of therapy than among the untreated

patients. However, definite clinical improvement followed shortly after the institution of treatment. Fifty-three children were treated with sulfanilamide. The 23 (43%) who were cured were treated for an average of 9½ days. This drug gave definitely better results than would be expected without treatment.

As a result of the foregoing observations, it seems likely that many of the epidemics of vaginitis reported in the past were not due to the gonococcus. There is further evidence that this infection is not as contagious as has been heretofore believed. In the vaginitis ward of a hospital there were children with acute gonococcal vaginitis, children who were cured and being observed for proof of cure and others who had been admitted to the ward for observation but were later shown not to be infected. No restrictions were placed on these children, and they were not isolated one from another. Over a period of years no instance of disease in the non-infected children was observed. Furthermore, during 2 different periods of several months all the children in the ward used the same toilets without causing new infections. As many as 8 infected children with profuse vaginal discharge were placed on the same toilet in rotation, and several cultures were made of material taken from the toilet seat. On only 1 of 18 occasions were gonococci recovered, and then only a few colonies could be found in 1 culture. As far as we know, no instance of transmission of the disease by way of the toilet seat has ever been proved. Investigation of parents and siblings revealed that the probable source of infection in the majority of cases was an infected adult in the home. Of a group of parents who prior to examination believed themselves healthy, 50% were found to be infected. Another important method of transmission that was disclosed is associated with sexual curiosity and experimentation. Of infected girls between the age of 6 years and puberty, 35% admitted sexual contacts. It may be concluded that the transmission of the disease requires inti-

mate contact between infected adult or child and non-infected child. Contaminated fomites, such as rectal thermometers, enema tips, diapers, towels and linen may possibly be factors in the spread of the disease. It is recommended that children not be excluded from school because of gonococcic vaginitis except during the stage of profuse discharge. Children who must be hospitalized because of complications or the occurrence of concurrent diseases need not be placed in separate isolation wards but may be treated for the complicating factor without regard to the vaginitis. Treatment with sulfathiazole would soon make such children non-infectious. It must be remembered that during the first few days aseptic technique should be practiced by the nursing staff. In the care of infected children, instruments and fingers come in intimate contact with the genitals of the patients and if not thoroughly cleansed may possibly infect another child.

While gonococci cause an endocervicitis and little actual vaginitis in the adult, the *Trichomonas vaginalis* causes a vaginitis and little if any endocervicitis. According to Brady and Reid⁴ the characteristic lesion is most often seen in the upper posterior part of the vagina just behind the cervix. One not infrequently sees in this area minute red spots, giving the upper posterior vaginal wall a strawberry-like appearance. The trichomonas is a protozoon with actively moving flagella at one extremity and an undulating membrane. The latter cannot always be seen as easily as the flagella. These organisms are larger than an ordinary pus cell and yet smaller than the epithelial cells which line the vagina and which can always be seen in vaginal smears. The trichomonads are very motile. Under the microscope their flagella can be seen moving rapidly. The technique for demonstrating these organisms is as follows: The gloved finger is inserted high in the vagina behind the cervix and a drop of the secretion taken on the gloved finger. This is mixed with a little normal salt solution and the prepa-

ration examined at once. The organisms can be seen under low or high grade power. It is not necessary to stain them. In some women, smears examined in the intermenstrual period may fail to show the organisms, while those taken immediately before or after a period will reveal them. This is what often happens. A woman comes to a doctor complaining of a leukorrheal discharge. He thinks of endocervicitis, polyps, carcinoma and many other gynecologic conditions as being the possible cause of the discharge. He at once puts green-soap or some other lubricant on his fingers and makes a pelvic examination. After his examination has failed to demonstrate any of the conditions mentioned above he then thinks of the possibility of a vaginitis due to the *Trichomonas vaginalis*, takes smears, looks at the material under the microscope and fails to see the organisms. This may be due to the fact that the green-soap on his fingers killed the trichomonads which were in the superficial tissues and by which the diagnosis could have been made. It is advisable to take smears for *Trichomonas vaginalis* as the first step in the study of all patients complaining of leukorrhea, pruritus and dyspareunia. Another factor that sometimes interferes with the diagnosis of trichomonas infections and also that of gonorrhea is that many women through a natural sense of cleanliness will take a douche immediately before coming to a doctor's office and thus prevent the physician from making the diagnosis. Although there have been many treatments recommended for *Trichomonas vaginalis* vaginitis, they may be divided into 2 groups based on what it is hoped the treatment will accomplish. In the first an effort is made to destroy all the protozoa by the use of antiseptics. In the second group of treatments less attention is paid to antiseptics than to measures which it is hoped will restore the normal defenses of the vagina. In general, this defense mechanism of the vagina is believed to depend primarily on 3 conditions: (1) that the vaginal

secretion remains at its normal low pH; (2) that the Döderlein or vaginal lactobacilli are present in sufficient numbers to form lactic acid and finally that there is sufficient carbohydrate, perhaps in the form of glycogen, in the vaginal epithelial cells or spaces between the cells to afford adequate nourishment for the continued growth and activity of the Döderlein bacilli. Being rather discouraged by the results obtained from the numerous preparations that had been recommended for the treatment of vaginitis due to the *Trichomonas vaginalis* Brady and Reid decided to try to build up the vaginal defense by carrying out several measures at once. Not only was nourishment suitable for the growth of Döderlein's bacillus to be introduced into the vagina but also viable lactobacilli. As soon as the diagnosis is made a bivalve speculum is introduced into the vagina, the cervix inspected for complicating endocervicitis and Skene's and Bartholin's glands inspected for possible involvement. The vagina is then dried with cotton and 2 lactobacillus tablets inserted high in the vagina in the posterior fornix behind the cervix. The vaginal orifice is then plugged with a tampon of non-absorbent cotton. When the patient returns on the next day the tampon is removed, material taken from the vagina for microscopic study and the treatment carried out on the preceding day repeated. On this second visit practically every patient will report that the itching has been much less, and it is very unusual to be able to demonstrate organisms at this time. Such office treatments are repeated daily for from 4 to 6 days. The patient is then told to insert 1 lactobacillus tablet high in the vagina each night. She is told to take douches only if she becomes uncomfortable from unabsorbed particles of the tablets coming out of the vagina and causing irritation. A white vinegar douche (5% acetic acid) is recommended in a strength of from 2 to 4 tablespoonfuls to 2 quarts of water. Two douches a week are usually sufficient. This home treatment is continued from 3

to 6 weeks and longer if necessary. However, if the organisms promptly disappear and show no immediate tendency to recur, the tablets need be used only every other night. It is especially important that they be used while the patient is menstruating, as that is, of course, the time when the vaginal defenses against the trichomonads are weakest. They are enthusiastic about the prompt results which they have obtained with the lactobacillus tablets, and have had numerous patients go without treatment for from 3 to 6 months in order to prove that they have really been cured of the infestation. Nevertheless they feel that every woman who has had a trichomonas infection should continue for considerable time to take either acetic acid douches or to use the lactobacillus tablets for a few days each month around the time of the menstrual period. In fact, no matter what treatment is carried out for vaginitis due to the *Trichomonas vaginalis* it should be repeated at each menstrual period for from 6 months to 1 year.

The type of vaginitis which is seen in elderly women and usually termed *senile vaginitis* is due to a lack of female sex hormone. According to Abarbanel, Arnow and Goodfriend,¹ this syndrome, which is so frequently accompanied by vulvar pruritus, is a part of the process of aging of the individual, and the entire patient must be treated, and not just one of her symptoms. Other constitutional and local causes must be excluded. Supportive treatment includes a well-balanced, properly cooked diet, rich in vitamins and minerals, as well as small doses of desiccated thyroid. At first the patient is instructed to douche twice daily while lying flat on her back in the bathtub, using 2 quarts of a lukewarm solution containing 3 to 4 ounces of ordinary household vinegar. If relief is not evident in 2 to 4 weeks, local therapy with an ointment containing 5 mg. of diethylstilbestrol per ounce is started, as this is the most effective and efficient means of administration. Approximately enough ointment to contain

0.5 to 1 mg. of diethylstilbestrol is rubbed thinly over the vulva once a day, while a small amount is smeared lightly over a vaginal cotton tampon before the latter is inserted. Acid douches are continued. When kraurosis vulvæ is pronounced, it may take several months to achieve complete relief. Pelvic examinations should be performed frequently to rule out a possible damming up of secretions, such as pyocolpos or hematometra. Uterine bleeding may occur at infrequent intervals, but it rarely is alarming. Sufficient ointment to contain 4 to 8 mg. of testosterone may be substituted once or twice a day for 1 week out of every 4. In fact, when the itching is extremely pronounced about the folds of the clitoris, testosterone ointment should be used daily, for this steroid seems to stimulate the surrounding glands to produce an oily secretion which serves to relieve the dry itching skin.

In the use of stilbestrol it should be remembered that there may be some unpleasant side reactions, the most common one being nausea. Careful study of these patients has brought to light several important factors, each of which must be carefully evaluated. The dose level is of prime importance. A few years ago it was reported from this clinic that the higher the dosage the greater was the incidence of side reactions. This has been amply confirmed. Equally important in evaluating nausea is the patient herself. Analysis of the latter reveals that 2 broad groups are recognizable. The first group is composed of patients in whom nausea may be considered as being incidental in nature. It includes those who are unable to take any type of oral medication including placebos. This group also embraces those patients who become nauseous with their flushes, for not infrequently the flushes may be accentuated at the start of treatment, thus aggravating the nausea. The nausea disappears as the flushes are relieved. These women are particularly liable to be nauseous on arising, a sort of "morning sickness" of the climacteric. The

second group comprises those patients in whom the nausea may be considered as a true side reaction. In this group the incidence of nausea is clearly related to the dose level. Further study disclosed that patients with a previous history of sensitivity to fried and fatty foods are much more prone to develop nausea at a given dose level than those with a previously negative gastro-intestinal history. This was shown to be statistically significant. Just why patients with a suggestive "gallbladder syndrome" are so much more likely to develop nausea when receiving diethylstilbestrol or estradiol remains to be clarified. It has been reported that estrogen may bring about a delay in the emptying time of the gallbladder. Such an effect, if confirmed in the human being, would serve to explain the increased nausea in the "gallbladder syndrome" patients, for they would tend to be more sensitive. The management of these patients should include administration of chologogues. Two teaspoons of magnesium sulfate once or twice a day are usually effective without causing cramping or diarrhea. Mild mercurous chloride, crude bile salts or purified bile acids may also be used. The nausea experienced by patients with a previously negative gastro-intestinal history does not usually present much difficulty. Its incidence may be considerably reduced by starting with a small dose level, 0.1 to 0.25 mg., and then raising it gradually if necessary. Administration of chologogues is also helpful. With the majority of these patients the nausea is usually transient, disappearing in spite of continued treatment. A word should be said about dosage. One mg. of oral diethylstilbestrol daily is approximately equivalent to injecting either 1 mg. of estrone (theclin) daily or 1 mg. of estradiol benzoate about every 3rd day. Clearly, then, a daily dose of 1 mg. is a relatively large dose, especially when it is recalled that, in contrast to estradiol and estrone, stilbestrol is not inactivated by the liver. Consequently a much higher amount of active estrogenic substance is

available to the body. Furthermore, it takes from 3 to as much as 12 days for the human being to excrete a given dose of diethylstilbestrol in contrast to the 2 or 3 days required for estradiol and estrone. In short, a cumulative effect occurs, so that even 0.1 mg. daily of oral diethylstilbestrol is not such a small dose after all.

Vaginal Medication. The value of vaginal medication has often been questioned since it would seem that the length of contact of the medicament with the tissues must be brief. An interesting study of this subject has been made by Rakoff and Casper,¹⁴ who state that, when properly administered the vaginal douche is admittedly an excellent method for bringing heat to the inflamed tissues or for cleansing the vaginal tract. It needs only to be added that as a method for medicating the vagina the douche is an inadequate one indeed, since the solution remains within the vaginal tract for so brief a time and what little medicament remains is rapidly diluted by the vaginal and cervical secretions and soon drained away. The swabbing or painting of the vagina offers some advantages over the douche in that the medication can be more thoroughly applied and often in higher concentration than is possible with the douche. Tampons saturated with medicated solutions or introduced into the vagina after the medication has been applied help to prevent the "messiness" which occurs when such solutions drain from the vaginal orifice, but since most of the medicament soon becomes absorbed in the body of the tampon, it is doubtful whether the tampon prolongs the period of useful medication. Relatively scant attention has been given to the use of water-dispersible jellies in the treatment of vaginal infections despite their widespread intravaginal use for contraceptive purposes. This is rather surprising since the jelly has much to commend it as a vehicle for intravaginal medication. Essentially, the jelly is a mixture of gums. It can be made water-dispersible so that it will mix easily with the vaginal secretions. Within the jelly

most any type of medicament can be intimately incorporated in various concentrations. After unsatisfactory experimentation with various techniques of demonstrating the manner in which jellies and other types of medication behave after introduction into the vagina, the value of roentgenology with regard to this problem was anticipated and subsequently confirmed. For this purpose they employed a water-dispersible jelly made up with a tragacanth-acacia-glycerin base adjusted to pH 4.5 with acetic acid. Into this was incorporated a radiopaque substance, such as barium sulfate (15%) or lipiodol (12.5%). When 5 cc. of the jelly was introduced into the posterior fornix under fluoroscopic control, the jelly was seen to spread at once over the cervix and into the lateral fornices while a small amount spread down towards the middle third of the vagina. In this case, films made at 30 minutes and at 1½ hours show that, although the jelly was slowly spreading, most of the opaque media still surrounded the cervix despite the fact that the patient was permitted to walk about. Generally, the jelly appeared at the introitus in from 1½ to 4 hours, but as late as 12 hours a considerable proportion of the jelly was still present, spread over the mucosa. Even when the jelly is purposely introduced into 1 of the lateral fornices, it is interesting to note that it spreads to cover the cervical os—a factor of particular importance from the contraceptive standpoint. Also, when the jelly within the vagina is mechanically agitated with a large test-tube to simulate coitus, it is noted that although further spreading is facilitated the jelly is sufficiently cohesive to remain as a good cervical barrier. The amount of jelly employed is a factor of importance which must be determined by the purpose for which it is to be used, the capacity of the vagina, its elasticity, and the degree of relaxation of the surrounding tissues. Although 5 cc. of jelly appears sufficient to act as a good cervical barrier even after 30 minutes, better spreading is obtained in the parous vagina

with 10 cc. In multipara with marked relaxation of the vaginal walls, the vaginal vault can easily retain 20 cc. and as much as 45 cc. will remain in the upper two-thirds of the vagina and will be retained in the vaginal tract even when the patient assumes the erect posture.

For several years they have successfully employed various types of water-dispersible jellies in the treatment of certain vaginal disorders. Buffered acid jellies were water-dispersible with pH ranging from 2 to 5 and were employed in the treatment of various specific bacterial infections, but particularly for the so-called "non-specific" bacterial infections. In most instances the latter result from disturbances in vaginal biology associated with reduced vaginal acidity, thus favoring the replacement of Döderlein's lactobacilli by a variety of other organisms. In a majority of these cases a jelly with pH 4 proved most efficacious. Acid jellies containing stilbestrol or the natural estrogens were particularly beneficial in the treatment of vulvovaginitis in children, both gonococcal and "non-specific," and also in atrophic vaginitis in menopausal women or younger women with ovarian deficiencies. Sulfonamide jellies containing various concentrations of the sulfa compounds are well tolerated and the absorption of the drugs from the vagina is very slow. The results by this method are not as good as when the sulfonamides are insufflated into the vagina as a powder. As a form of medication the authors found suppositories in general to be inferior to jellies. In most instances the size of the suppository is small as compared with the capacity of the vaginal tract; the suppository is comparatively heavy and often gravitates to the lower part of the vagina before it has melted. The introduction of medicaments in powder form has become very popular in recent years. In the treatment of vaginal trichomoniasis especially, the "dry" method of treatment is preferred, usually consisting of the introduction of trichomonacidic chemicals in a drying base such as kaolin. For this

method of medication one may use compressed tablets, large gelatin capsules, or the powder may be blown into the vagina with an insufflator. They have found the latter to be the only really efficient method of completely covering the vagina with a powder. Although some of the powder thus introduced begins to be washed out within a few hours, much of it usually remains *in situ* for 24 hours or more.

The use of powders in the vagina should be a harmless procedure, but Martland¹⁰ reports 2 deaths occurring after vaginal insufflation of medicinal powders for the relief of pruritus vulvæ. In the first case a virginal and cribriform hymen played an important rôle in the causation of the air embolism. The doctor, believing he was spraying powder over the external genitals, must have unknowingly held the glass tip of the insufflator directly over the largest opening in the hymen and have blown powder and air into the vagina. The air entrapped in the vagina was forced into the uterine cavity. The exact point of entry of air into the venous circulation could not be demonstrated. The fact that the patient had just passed a menstrual period favored engorgement and distention of the uterine veins. The second woman was 6 months pregnant. In this case the metal end of the insufflator must have rested against the soft cervix of the pregnant uterus and considerable powder and large amounts of air were blown directly into the uterine cavity. The main purpose of the insufflators is to dilate and smooth out the folds in the vagina so that the powder may be sprayed on the mucosa. It is obvious that the sudden blowing up of the vagina with air under excessive pressure is not without danger. The engorgement of the endometrium around the menstrual periods, open veins after uterine enurettage and the soft cervix of a pregnant uterus all might favor air embolism during such insufflations.

POSTERIOR VAGINAL HERNIA. The changes in the normal anatomy of the pelvic floor which permit a herniation of the cul-de-sac into the upper vagina pro-

duce a condition which has been described in the literature under the titles of posterior vaginal hernia, enterocele, cul-de-sac hernia, Douglas' pouch hernia, enterocele and high rectocele. It is characterized by the protrusion of a peritoneal sac through the cul-de-sac of Douglas which dissects its way between the vagina and the rectum and presents as a mass in the vagina. In discussing the mechanism of this defect Dixon⁷ states that it is of rare occurrence because the obliquity of the pelvic cavity allows the force of intra-abdominal pressure to expend itself to some extent on the bladder, symphysis and anterior abdominal wall, thus protecting the pelvic floor. The strain and trauma of childbirth are of importance in the etiology. But some congenital defect must play an important part since the condition is so rare in multiparous women, but nevertheless occurs in those who have not borne children. The symptoms complained of by the patient are a sense of weight and pressure in the pelvis, and a variable degree of bulging in the vagina. Where the sac is well developed, a mass may protrude from the vagina on standing or straining, which usually disappears when the patient lies down. Many of the reported cases had had previous operations for repair of the pelvic floor with a recurrence of the bulging as soon as the patient got up. This is always suggestive of such a hernia. Examination with one finger in the rectum and one in the vagina will differentiate the condition from a rectocele, which may coexist, as it will show that all the protrusion is not due to the rectocele. In cases where rectocele does not exist this maneuver helps to establish the fact that the protrusion originates behind the cervix, and if the patient is asked to strain, it will determine the presence of abdominal contents in the protrusion. The treatment of this condition is surgical, since palliation by pessaries does not afford relief. The same principles apply here that apply to the treatment of hernia elsewhere, namely isolation of the sac, disposition of the sac

and closure of the point of egress of the hernia from the abdominal cavity. There are 2 avenues of approach. The abdomen may be opened, the sac inverted into the abdomen and disposed of, and the cul-de-sac obliterated. Such an approach may be necessary if the abdominal contents are adherent in the sac but where this is not necessary, the vaginal approach is more desirable. This consists in opening the posterior vaginal wall from the cervix to the perineum, dissection of the sac from the rectum and surrounding tissues, ligation of the neck of the sac and excision of the excess, anchoring the stump behind the cervix and obliteration of the cul-de-sac by approximating the uterosacral ligaments. The remaining tissues are approximated and a high perineorrhaphy completes the operation.

Phaneuf¹³ states that a hernia of this type may follow vaginal hysterectomy for the treatment of prolapse if the cul-de-sac is not closed. This may be prevented by approximating the uterosacral ligaments to each other in their entire length when performing vaginal hysterectomy. In addition to the 2 methods of treatment which have previously been described, he suggests the use of colpocleisis, or closure of the vagina, when the hernia is large and there are contraindications to laparotomy.

TUMORS. The rarity of *vaginal myomas* is pointed out by Bennett and Ehrlich² who found only 9 cases among more than 50,000 specimens in a gynecologic laboratory to which they have added 3 additional cases. Most of the reported cases are in white women contrasting strikingly with the racial incidence of uterine myomas which are almost 3 times as common in colored women. The tumor usually presents in the vagina as a non-pedunculated ovoid mass covered with smooth intact mucosa and has no characteristic appearance which would differentiate it from a vaginal cyst or cystocele. In this series the tumors were usually small, varying from 1.5 to 4.5 cm. in the greatest diameter, although very large tumors

have been reported by others. The lesion is usually single and may develop at any point in the vaginal wall, although more than half of the tumors reported have been on the anterior wall. They are firm in consistence and the symptoms depend on the size and location of tumor. Pressure on the urinary organs will give urinary symptoms, either retention or frequency, while some patients complain of a protruding mass of dyspareunia. If degenerative changes have occurred in the overlying mucosa, there may be a vaginal discharge or bleeding, at times simulating a malignant tumor. The treatment of this condition is simple excision which is usually easily carried out.

Another rare tumor is *sarcoma* of the vagina which also seems more common on the anterior vaginal wall. In presenting 2 of these cases Diehl and Haught⁶ state that the tumor is friable, bleeds easily on manipulation, grows rapidly, soon filling the entire vagina and presenting at the introitus as a polypoid mass of

necrotic tissue. Microscopically the tumor is composed of an edematous, myxomatous stroma through which are dispersed, in varying degrees, spindle and stellate cells. Bloody vaginal discharge is usually the first symptom, frequently associated with pain and itching of the vulva and vagina. As the condition progresses, pain becomes more intense because of pressure. The pelvic mass first encroaches upon the bladder, resulting in frequency, incontinence and infection. Hematuria often develops indicating involvement of the bladder mucosa. Later the rectum becomes involved causing tenesmus, constipation and rectal bleeding. Cachexia, anemia and edema of the lower extremities are terminal signs. Distant metastases are extremely rare, the lung and kidney being the only 2 sites reported. The treatment of this condition is most discouraging. Because of its extremely malignant nature and rapid growth, the tumor is soon beyond the realm of response to surgery or irradiation.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF APRIL 15, 1947

Preliminary Tests of Sudden Upward Acceleration on Sitting Men. D. T. WATTS, PH.D., E. S. MENDELSON and A. T. KORNFIELD (Aero-Medical Equipment Lab., Naval Air Exptl. Station). Of aviators attempting bailouts from fighter planes during the war 18 to 25% were fatally injured due to the difficulty of successful emergency escape. The most feasible method of separating the pilot from present planes utilizes an ejectable seat, driven up rails by a powder exploded catapult. Such seats were developed by the Germans and improved by the British, for use up to about 20 "G". The American Army and Navy have been collaborating in their perfection.

The test subject is fastened into a pilot's seat at the base of a 105 foot test tower, up which the seat may coast, but down which it must be lowered. Ejection guns for use in aircraft are mounted between the seat and the base of the tower. The time phenomena measured are pressure in the gun, seat displacement, muscular tension, and accelerations on the seat and on the subject's head, shoulder and hip. Performance of a number of catapults has been tested with dummies. Correlations of ballistic and dynamic phenomena have led to the development of catapults capable of producing the highest safe velocities with a given length of stroke, or given velocities with the shortest safe length of stroke.

Motion pictures of subjects using arm rests, or a face-restraining curtain pulled down by the hands, show some incipient hazards of upward ejection. The face curtain appears much safer. The dynamic response in the coupled system, man-cushion seat, points to a minimum safe time interval of 0.013 second for the

application of acceleration. Acceleration levels applied to the system by the catapult in shorter periods of time result in higher levels on the man. A new seat catapult has been developed at NAES for ejection at the most rapid rate of acceleration which will not result in a dynamic response factor greater than one, and which will induce maximum accelerations only 75% of those in former systems.

Glycolysis of Different Hexoses in Brain Tissue in Connection With the Turnover of Adenosinetriphosphate (ATP). OTTO MEYERHOF, M.D. (Dept. of Physiol. Chem., School of Medicine, Univ. of Penna.).

Brain tissue as well as tumor tissue glycolyzes glucose much faster than fructose. But in cell-free enzymatic extracts both are metabolized with equal speed, which is moreover much higher than the glycolysis of tissue slices. (Q_{LA} about 50 instead of 15 to 10 in brain slices.) On the other hand the glycolysis in a homogenate of brain, which contains the disintegrated cell structures, resembles closely that of slices as well in the absolute value of Q_{LA} as in the difference of glucose and fructose.

These facts are explained by the distribution and affinities of two enzymes concerned with the turnover of ATP: hexokinase and ATP-ase. The latter enzyme is strongly adsorbed on the structural elements. In the complete homogenate it is ten times as concentrated as in the centrifuged extract, where the particles are removed. The concentration of added ATP in the homogenate drops to very low values in a few minutes because of the high activity of ATP-ase. The rate of glycolysis is mainly controlled by the

reaction between the sugar and ATP in presence of the enzyme hexokinase. First, the speed depends over a wide range on the concentration of ATP; secondly, the influence is different for glucose and fructose. With higher ATP concentrations (over 20 γ labile P of ATP per cc.) the affinity of glucose and fructose is the same, but for low ATP concentrations (2 γ to 8 γ labile P per cc.) the affinity for fructose is much less. In this case the rate of glycolysis of fructose is much smaller than for glucose. To prove this point in tissue extracts, it is necessary to use very little hexosediphosphate for priming the reaction; otherwise the excess of hexosediphosphate serves as P donor for rephosphorylation of ATP.

From these experiments it follows for the living brain- or tumor cell, where the different behavior of glucose and fructose is quite outspoken, that the active concentration of ATP responsible for the turnover is surely quite low, and amounts to only some per cent of that found by chemical analysis. Probably the bulk of ATP is either separated from the reacting sugar by cell interfaces and immobilized in this way, or it is bound to inert protein and therefore unable to react.

Experimental Metastasis of Frog Carcinoma. BALDUIN LUCKÉ, M.D., and H. G. SCHLUMBERGER, M.D. (Dept. of Pathology, Univ. of Penna.).

Vestibular Disturbances Produced in Animals by Streptomycin. JOSEPH E. HAWKINS, JR., PH.D., and CHARLES W. MUSHETT (Merck Institute for Therapeutic Research, Rahway, N. J.).

The chronic neurotoxic action of streptomycin in rabbits, dogs and cats is

similar to that occurring in some patients receiving prolonged treatment with streptomycin. In animals a gradual loss of nystagmus in response to rotation occurs during treatment with large doses of the drug by subcutaneous injection. This effect has been studied quantitatively by electrical recording of pre- and post-rotational nystagmus in unanesthetized animals. The rate and duration of both optokinetic and vestibular nystagmus are reduced, and in the rabbit both types of nystagmus may be abolished. In the cat the loss of nystagmus may progress even after the drug is discontinued. No recovery of nystagmus has occurred in animals observed for 4 months after the drug was stopped.

In addition to ataxia and other disturbances of equilibrium which occur in all 3 species, cats show difficulty in maintaining fixation upon a single object in the field of view.

Although histological studies have thus far revealed no lesions in the nervous system attributable to streptomycin, the experimental results suggest that the streptomycin may act not only on the peripheral vestibular apparatus, but also possibly upon the vestibular nerve, the medullary vestibular centers, and cerebellar and mid-brain centers. Electrophysiological studies of auditory function show that streptomycin decreases the responsiveness of both the cochlea and the auditory nerve.

The behavior of dogs and cats which had received streptomycin for 2 to 3 weeks is illustrated in a motion-picture film. This shows the changes in gait and posture occurring in dogs, the animals' inability to maintain their balance on a tilt-table, and the absence of nystagmus after rotation. Even more dramatic disturbances of equilibrium are shown in cats.

BOOK REVIEWS AND NOTICES

MODERN MANAGEMENT IN CLINICAL MEDICINE. By F. KENNETH ALBRECHT, M.D., S.A., Surgeon, U. S. Public Health Service; Kansas State Tuberculosis Consultant; formerly Clinical Director, U. S. Marine Hospital), Baltimore, Md. Foreword by ALPHONSE McMAHON, COMMODORE, MC, USNR, Chief of Medicine, U. S. Naval Hospital, Bethesda, Md. Pp. 1238; 237 ills.; 11 color plates. Baltimore: Williams & Wilkins, 1946. Price, \$10.00.

THIS volume represents a new and exceedingly practical approach to the presentation of information for the diagnosis and treatment of disease. Intended for the office, not the library, it has the salient data in readily available form. Good use is made of comparative tables, for instance, in differential diagnosis. Techniques of treatment are described fully and well. Drugs are mentioned by their trade names, with information on their composition.

The first chapter deals with the case history, including its medico-legal aspects. In this, as in succeeding chapters, the author makes use of long and detailed forms for use in history taking and physical diagnosis. The second chapter takes up nutrition and the vitamin deficiencies, and is very well done. Other chapter topics include gastrointestinal diseases, diseases of the heart, peripheral vascular disease, diseases of the kidneys, venereal diseases, diseases of the respiratory system, arthritis and allied conditions, endocrinology for the general practitioner, diseases of allergy, diseases due to intoxications, physical agents and poisons; infectious diseases, tropical diseases of post-war importance, nervous and mental diseases, diagnosis and treatment of common skin disorders, chemotherapy, geriatrics, the care of the ambulatory patient. The chapter on clinical laboratory medicine, by Seward E. Miller, M.D., gives the indications for and the interpretation of results of tests. The chapter on common procedure and diets includes the techniques of thoracentesis, abdominal and pericardial tap, intravenous injections, transfusions, lifting and turning patients, the use of counter-irritants.

Criticisms of minor importance are: inadequate handling of some subjects (disseminated lupus rates only 74 words); a number of consistently misspelled words (for example, Van den Burgh); scarification with a needle is the way *not* to do a cutaneous test for allergy; intracutaneous is a proper term, *not* intradermal; the author uses "regime" when he means "regimen," and "temperature" for "fever;" a 100-grain dose of nitroglycerine will not occur in the next edition.

Commendable are the format with parallel columns instead of the solid page, the many excellent illustrations, and the fine color plates. The book should have a wide appeal.
R. K.

PATHOGENICITY OF CERTAIN SEROLOGICAL TYPES OF B. COLI. By SVEN SJOSTEDT, Univ. of Lund. Pp. 148. Lund, Sweden: Hakan Ohlssons Boktryckeri, 1946. Price not given.

THIS thorough, careful study of 1331 strains of *E. coli* was based upon the serologic classification of Kauffmann, of Knipschildt and of Vahlne. Cultures derived from appendicitis, peritonitis, urinary infections, feces of normal persons, etc., were classified according to their O, K (heat-labile somatic or capsular) and H antigens. Mouse toxicity, hemolysis, necrotizing properties and resistance to phagocytosis were determined. The toxicity of individual capsulated strains of the same serotype are alike in toxicity, irrespective of their origin. Capsulated forms are considerably more toxic than corresponding non-capsulated forms. Hemolysis was associated with certain definite serotypes and there was some correlation between hemolysis and necrotizing ability. In general, cultures which were hemolytic and produced skin necrosis were highly toxic. Strains of the same serotype possessed the same resistance to bactericidal properties of normal human blood, different serotypes varied widely. This resistance had no relation to toxicity. Resistance to phagocytosis was dependent upon a well-developed capsule and phagocytosis was enhanced by the addition of appropriate K serums but not by O serums. There was

little correlation between toxicity and resistance to phagocytosis.

A correlation of clinical histories of cases from which cultures were derived and the properties of the strains isolated led to the conclusion that capsulation, hemolysis and necrotizing capacity are significantly related to toxicity and pathogenicity. Capsular antigens appeared in the urine of patients affected with coli peritonitis. P. E.

THE TREATMENT OF BRONCHIAL ASTHMA.

By VINCENT J. DERBES, M.D., Instructor in Medicine and in Preventive Medicine, Tulane University of Louisiana School of Medicine, Director of the Department of Allergy, Ochsner Clinic; and HUGO TRISTRAM ENGELHARDT, M.D., F.A.C.P., Instructor in Clinical Medicine, Baylor University College of Medicine, Houston, Texas, Adjunct in Medicine, Jefferson Davis Hospital; formerly Instructor in Medicine, Tulane University. With chapters by a panel of Contributors. Pp. 466; 61 ills. Philadelphia: J. B. Lippincott, 1946. Price, \$8.00.

ENTITLED "The Treatment of Asthma," the book attempts a complete survey of all phases of the subject in an introduction and 23 chapters. The introduction and 15 chapters are by 17 writers other than the 2 authors listed on the title page, who have done only 8 chapters, themselves. This procedure was presumably prompted by the wish to get the views of experts in their several fields. The principle is applicable to textbooks of medicine, but would hardly seem justified to the extent of 19 authors to discuss a single disease. The result in this instance is not a happy one. In general, there is considerable duplication and poor balance. There are some very good chapters such as the history (Major), statistics (Dublin and Marks), anatomy and physiology of the respiratory tract (Burch), pollen survey (Durham), differential diagnosis (Soderman). Others leave much to be desired, such as the description of the disease, which is quite inadequate; the rôle of foods in asthma, which merely cites all reported instances of foods as allergens but gives no figures on incidence or relative importance, and is uncritical, as in its inclusion of salt as an accepted allergen; the bacterial, epidermal and miscellaneous factors are skimpily handled, as is the chapter on the oto-

laryngologic aspects. Some of the material is irrelevant, as for instance the inclusion of malaria and amebiasis in the chapter on parasitic agents and asthma, and similarly, the chapter on cardiac asthma could largely be dispensed with. The chapter on psychogenic factors is written with far less insight into matters allergic than most allergists have into psychiatry; those who would challenge this statement should see if the references at the end of the chapter are a fair sample of contemporary opinion. The book is not recommended. R. K.

ACIDOSIS. Clinical Aspects and Treatment With Isotonic Sodium Bicarbonate Solution. By ESBEN KIRK, M.D., Chief Physician, Medical Service, Holstebro District Hospital, Holstebro, Denmark. Pp. 222; 21 ills. Copenhagen: Einar Munksgaard; London: Heinemann, 1946. Price not given.

THE author, at one time a member of Dr. Van Slyke's staff at the Rockefeller Hospital, has been active in encouraging in Denmark the quantitative study of clinical acidosis and its therapy with alkali. The Danish edition of the present work appeared in 1942.

The occurrence of acidosis in some 30 or 40 different clinical conditions is described. These conditions are illustrated with 54 brief case reports which add much to the value of this study. J. A.

QUANTITATIVE CLINICAL CHEMISTRY. INTERPRETATIONS. VOL. I. By JOHN P. PETERS, M.D., M.A., Professor of Internal Medicine, Yale University School of Medicine, and DONALD D. VAN SLYKE, Ph.D., D.Sc., Member of the Rockefeller Institute for Medical Research. 2nd ed. Pp. 1041; 62 ills. Baltimore: Williams & Wilkins, 1946. Price, \$7.00.

THIS 2nd edition of a well-known book includes in this volume only half of the field of the original "Interpretations," which is now to be expanded to 2 volumes.

The authors have divided their activities; this present volume is mainly the work of Peters, as will be most of the 2nd volume of "Interpretations."

As in the original edition, every statement is based on some specific piece of work for which the reference is given; yet the author

has skillfully woven these separate contributions to our knowledge into a critically evaluated account which gives the reader an integrated picture of the subject being presented: a notable achievement.

Of the approximately 4600 references, about three-fourths seem to the Reviewer to have been published since the date of the 1st edition. It is obvious, therefore, that this volume is essentially a new writing upon current knowledge of the fields covered. These fields include energy metabolism, carbohydrate, lipids and protein metabolism.

Both for the student of the preclinical sciences of physiological chemistry and physiology, and, of course, for the worker in the clinic, this volume will constitute an authoritative text and an indispensable book of reference.

J. A.

VOCATIONAL AND PROFESSIONAL MONOGRAPHS—PHYSIOTHERAPY. By THOMAS FRANCIS HENNESSEY, M.D., Dean and Director, Massachusetts School of Physiotherapy, Boston. Pp. 23. Boston: Bellman Publ. Co. Price, \$7.75

THIS is the 65th in a series of 75 pamphlets which deal with various occupations. Their purpose is to aid individuals in the choice of a career. The author, whose biographical sketch appears in the front of the pamphlet, is a physician who has evidently been well trained in Physical Medicine and is competent to discuss the possibilities of Physical Therapy as a vocation. Throughout, the term Physiotherapy is used instead of the more acceptable designation, Physical Therapy. Non-professional individuals who practice Physical Therapy are referred to as Physical Therapy Technicians and the term Physiotherapist is reserved for physicians who specialize in this field. In accordance with the latest recommendations, the term "technician" should be dropped and replaced by the title Physical Therapist, and physicians who specialize in Physical Medicine should be called Physiatrists.

After a brief account of the history of Physical Therapy and the effects of war upon its development, the present demand for Physical Therapists is stressed. In the discussion of schools for the training of physical therapists several misstatements occur. The American Medical Association within the last 3 years has approved not more than 32 physical therapy schools, and not 80 to

100 as stated. The official statement of the Council of Medical Education and Hospitals of the American Medical Association of April 18, 1946, lists only 21 schools as offering acceptable training. The school of which the author of the pamphlet is Dean and director is not numbered among them. It is stated that graduates from schools of Physical Therapy, when they become 21 years of age automatically become members of "the national association of physiotherapy technicians." More correctly stated, graduates may be elected to the American Physical Therapy Association if their preliminary education and academic record meets the exacting requirements of that organization; to become a member of the American Registry of Physical Therapy Technicians necessitates a separate examination.

The author refers to "Hemo-Irradiation" as "the most outstanding technique of recent years," whereas the procedure is of doubtful clinical value and the instrument required for this technique has never been approved by the Council of Physical Medicine of the American Medical Association.

The pamphlet, which stresses the economic rather than the scientific advantages of Physical Therapy as a career, can hardly be regarded as an authoritative discussion of a field of therapeutics that is constantly growing in importance.

G. P.

TREATMENT BY ION TRANSFER. By D. ABRAMOWITSCH, M.D., Physician in Charge of the Physiotherapy Department, Lincoln Hospital, New York City, and B. NEOUSSIKINE, M.D., Tel-Aviv, Palestine. Foreword by RICHARD KOVACS, M.D. Pp. 186. New York: Grune & Stratton, 1946. Price, \$4.50.

ION transfer (iontophoresis) is a branch of electrotherapy with which most physicians are unfamiliar. Too often, electrotherapy is thought of as "heat therapy," and the employment of the electric currents, other than for the production of heat, is either looked at askance or disregarded entirely. It is true, that until recent years, there has not been much precise knowledge as to the physics and the clinical applications of the galvanic current; but this ignorance is slowly being dispelled.

This volume answers many questions arising in the physician's mind, concerning ion transfer, and at the same time poses

others for solution. Perhaps the only satisfactory approach to these problems is through the collaboration of the physiologist, the bio-physicist and the clinician in Physical Medicine.

The book is recommended to the medical profession; especially Part 1, which deals with the physical characteristics of the electric current which is used for ion transfer. Part 2 deals with the treatment of individual diseases. Some of the techniques are given in considerable detail, while others are presented somewhat sketchily. The chapters devoted to facial palsy are of especial interest.

For specialists in Physical Medicine and their technical assistants, this stimulating little volume ought to be on the handiest shelf of the library. A large and valuable Bibliography is included. S. H.

HISTORY OF MEDICINE. By DOUGLAS GUTHRIE, M.D., F.R.C.S., Edinburgh. Pp. 448; 72 ills. Philadelphia, London and Montreal: Lippincott, 1946. Price, \$6.00.

GUTHRIE'S book adds a practical and readable text to the available short histories of medicine. In it the entire development of medical science is integrated in a single continuous story in which a good balance is preserved in the accounts of ancient, medieval and later medicine. The treatment of subjects in the successive chapters is in considerable measure biographical, but with an excellent sense of proportion in the selection of significant advances as represented by the work of distinguished physicians. The detailed story stops with Sir William Osler, whose influence upon medical science is well treated in the final chapter. There is brief mention in a chapter on military and naval surgery of some of the achievements of medicine and surgery in the period "between the wars," including sulfonamide and penicillin treatment and other developments of modern medical science. Medical students will find the chapters on "Specialism and Preventive Medicine" and "Journalism, Bibliography and Medical History" particularly useful for their assessment of these characteristic features of the modern period, which do not receive due attention in many of the other medical historical texts available. The illustrations are excellent. The book is recommended as a useful compendium for

those who wish to see medicine in a broad outline, and are not in a position to pursue it in detail through the encyclopedic texts.

E. L.

MEDICAL CLINICS OF NORTH AMERICA. May 1946. New York Number. Rheumatic Diseases. Pp. 243. Philadelphia: Saunders, 1946. Price, \$16.00 a year.

ARTICLES on rheumatic fever, rheumatoid, menopausal and pneumococcic arthritis, gout and Reiter's syndrome are presented by authorities in the field of rheumatic diseases. In particular, therapy of these varied disease states is emphasized. There are also separate papers on Roentgen irradiation, vitamins, physical medicine and orthopedics in the management of rheumatic diseases. On the whole this section ought to be a valuable adjunct to the practitioner who treats patients afflicted with rheumatic disorders.

A paper entitled "Hypertension Due to Arteriosclerosis, and Its Complications" contains several misstatements which should not be permitted to go unchallenged. The development of hypertension as a consequence of an arteriosclerotic lesion in one of the centers regulating blood pressure is more or less hypothetical and not a statement of fact. It is indeed remarkable that an enema of 16 ounces of water is likely to cleanse the small bowel in preparation for the administration of digitalis by rectum. It is also stated that pulsus alternans can be detected by "taking the diastolic blood pressure and when the lowest point is reached if one pulse beat is heard and the next one falls out, pulsus alternans is present." In the management of congestive failure the Karell diet is said to consist of 1000 to 1500 cc. of milk every 2 hours.

The Reviewer hopes that at least some of these errors are due to careless proofreading.

C. F.

NEW BOOKS

A History of Scientific English. The Story of Its Evolution Based on a Study of Bio-medical Terminology. By EDMUND ANDREWS, M.D. Foreword by ARNO B. LUCKHARDT, M.D. Pp. 342; 18 figs. New York: Richard R. Smith, 1937. Price, \$7.50.

Uterotubal Insufflation. By I. C. RUBIN, M.D., F.A.C.S., Clinical Professor of Gynecology, Coll. of Physicians and Surgeons, Columbia Univ. Pp. 453; 159 ills., 4 in color. St. Louis: C. V. Mosby, 1947. Price, \$10.00.

Genetics, Medicine, and Man. By H. J. MULLER, of Indiana Univ., C. C. LITTLE, of the Roscoe B. Jackson Mem. Lab., LAURENCE H. SNYDER, of The Ohio State Univ. Pp. 158; 30 ills. Ithaca: Cornell Univ. Press, 1947. Price, \$2.25.

Therapeutic Exercise. By F. H. EWERHARDT, M.D., Ass't. Professor of Physical Medicine, Washington Univ. School of Medicine, and GERTRUDE F. RIDDLE, B.S., R.N., R.P.T., Instructor, School of Physical Medicine, St. Louis Univ. Pp. 152; 8 figs. Phila.: Lea & Febiger, 1937. Price, \$2.50.

Die Hormonalen Aspekte des Fortpflanzungsprozesses. By DR. JULES SAMUELS, Chirurg-Frauenarzt. Pp. 152. Amsterdam, Holland: Holdert & Co., N.V., 1946. No price given.

Die Hormonversorgung des Foetus. By DR. JULES SAMUELS, Chirurg-Frauenarzt. Pp. 320. Leiden, Holland: E. J. Brill, 1947. No price given.

Tomorrow's Food. By JAMES RORTY and N. PHILIP NORMAN, M.D. Foreword by STUART CHASE. Pp. 258. New York: Prentice-Hall, 1947. Price, \$3.50.

Child Health. "The Practitioner" Handbooks. Edited by ALAN MONCRIEFF, M.D., F.R.C.P., Nuffield Professor of Child Health, Univ. of London, and WILLIAM A. R. THOMSON, M.D. Pp. 254. London: Eyre & Spottiswoode, Ltd., 1947. Price, 14 s, net.

Rehabilitation Through Better Nutrition. By TOM D. SPIES, M.D., Univ. of Cincinnati Studies in Nutrition at the Hillman Hosp., Birmingham, Ala. Pp. 94; 50 figs. Phila.: W. B. Saunders, 1947. Price, \$4.00.

NEW EDITIONS

A Text-Book of Pathology. By E. T. BELL, M.D., Professor of Pathology, Univ. of Minnesota. Contributors, B. J. CLAWSON, M.D., and J. S. MCCARTNEY, M.D. 6th ed., enlarged and thoroughly revised. Pp. 910; 500 ills. and 4 color plates. Phila.: Lea & Febiger, 1947. Price, \$10.00.

Obstetrical Practice. By ALFRED C. BECK, M.D., Professor of Obstetrics and Gynecology, Long Island College of Medicine. 4th ed. Pp. 966; 1058 ills. Baltimore: Williams & Wilkins. Price, \$7.00.

Nutritional and Vitamin Therapy in General Practice. By EDGAR S. GORDON, M.D., Ph.D., Assoc. Professor of Medicine, Univ. of Wisconsin. 3rd ed. Pp. 410. Chicago: The Year Book Publishers, 1947. Price, \$5.00.

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INDEX

A

- Abbott, William E., *see* Meyer, Frieda L., 160
- Adrenal medulla, Insensitivity to epinephrine in a patient with a functioning tumor of the, 324
- Adrenalin, Increased reactivity caused by, 331
- Aegerter, Ernest, and Robbins, Robert, The changing concept of myeloma of bone, 282
- Agglutination of hemolytic streptococci, Rheumatoid arthritis, V., 94
- Alimurung, Mariano M., *see* Molina, Richard D., 435
- Allergic manifestations, Histamine antagonists. IV. Pyridil-n/benzyl-dimethylethylenediamine (pyribenzamine) in symptomatic treatment of, 58
- Alsted, Gunnar, Studies on malignant hepatitis, 257
- Alvarez, Walter C., The migrainous personality and constitution. The essential features of the disease: a study of 500 cases, 1
- Aminoacetic acid, Use of. Specific dynamic action as a means of augmenting peripheral blood flow, 46
- Amylase levels during mumps: The findings in blood and saliva, 477
- Amyloidosis, Diagnosis of generalized, by the Congo red test; definite diagnostic criteria, 719
- Anemia, atypical, with spherocytes and target cells coexisting in the blood, 153
- pernicious, Treatment of, with synthetic *L. casei* factor, 694
- sickle cell. Recent progress of pediatric interest, 728
- Anemias, macrocytic, in relapse, Relative clinical and hematologic effects of concentrated liver extract, synthetic folic acid and synthetic 5-methyl uracil in the treatment of, 135
- Antibiotics, A routine method for the rapid determination of susceptibility to penicillin and other, 221
- Antithyroid effect, Further studies on the correlation of chemical structure and, 198
- Arnett, John H., Treatment of carriers of *Endamoeba histolytica* and other protozoa with carbarsone, chiniofon and vioform, 608
- Arthritis, rheumatoid. IV. Hemolytic streptococcus precipitin reactions, 87
- V. The agglutination of hemolytic streptococci, 94
- Ascitic fluid, human, The intravenous use of, in shock, nephrosis and allied conditions, 435
- Autonomic ganglia in man, The effects of blockade of the, with tetraethylammonium. Preliminary observations on its clinical application, 315

B

- B vitamins and protein, Changes in personality appraisal associated with a restricted intake of, 488

- Bacterial endocarditis, subacute, Experiences with penicillin and dicumarol in the treatment of, 300
- Barden, Robert P., *see* Pendergrass, Eugene P., 192
- Barnes, Allan C., Postpartum blood: its clotting mechanism and relationship to the peripheral blood picture, 463
- Bean, William B., *see* Eichna, Ludwig W., 641
- Beaser, Samuel B., Renal excretory function and diet in diabetes insipidus, 441
- (Benadryl), Dimethylaminoethyl benzhydryl ether hydrochloride, Some pharmacologic and clinical experiences with, 418
- Berry, Robert L., *see* Lyons, Richard H., 315
- Berryman, George H., *see* Henderson, Charles R., 488
- Birchall, Robert, Taylor, R. D., Lowenstein, V. E., and Page, Irvine H., Clinical studies of the pharmacologic effects of tetraethyl ammonium chloride in hypertensive persons made in an attempt to select patients suitable for lumbodorsal sympathectomy and ganglionectomy, 572
- Bismuth sodium tartrate, Further report on the use of, intravenously in the treatment of 203 additional patients with tularemia, 358
- Block, Frank B., The vagina, 737
- Blockade of the autonomic ganglia in man with tetraethylammonium. Preliminary observations on its clinical application, 315
- Blood, Postpartum: its clotting mechanism and relationship to the peripheral blood picture, 463
- pressure studies in 100 cases of coronary occlusion with myocardial infarction, 40
- volume studies, Nitrogen balance and, in man during and following repeated plasma transfusions, 160
- Blumberg, Nathan, and Schloss, Eugene M., The effect of circulatory factors on the bromsulphalein test in liver disease, 470
- Bondi, Amedo, Jr., Spaulding, Earle H., Smith, Dorothy E., and Dietz, Catherine C., A routine method for the rapid determination of susceptibility to penicillin and other antibiotics, 221
- Bone marrow, sternal, The significance of the myeloid maturation curve in material aspirated from the, 686
- Boyd, Eldon M., and Dingwall, R. W., The absorption and elimination of sulfadiazine administered as tablets, as a ground (micronized) powder and as microcrystals, 549
- The effect of sodium and potassium lactates upon the absorption and elimination of microcrystalline sulfadiazine, 557
- Boyd, Linn J., *see* McGavack, Thomas H., 418
- Bramante, P., *see* Marfori, L., 150
- Breitwieser, E. Ruth, Electrocardiographic observations in chronic cholecystitis before and after surgery, 598

- Bromsulphalein retention, The relationship of, to the fever of natural *P. falciparum* malaria, 81
 test in liver disease, The effect of circulatory factors on the, 470
- Brown, Hathorn P., *see* Landsteiner, Ernest K., 450
- Bruce, Robert A., and Slavin, Howard B.: A study of an outbreak of influenza B in Rochester, New York, 129
- Burgoon, David F., *see* Machella, Thomas E., 81
- B vitamins and protein, Changes in personality appraisal associated with a restricted intake of, 488
- C**
- Calcification, Disseminated, of the pancreas: Subacute and chronic pancreatitis, 290
- Cameron, D. Ewen, Increased reactivity caused by adrenalin, 331
- Campbell, Kenneth N., *see* Lyons, Richard H., 315
- Cancerous patients, The tyrosinase inhibiting action of serum from normal and, 655
- Capillary and arteriolar platelet thrombosis, Generalized, 585
- Carcinoma of the prostate, Observations on the treatment of, by orchidectomy, 450
- Cardiac murmurs, Clinical features of patent ductus arteriosus with special references to, 385
- Carotid sinus pressure in the aged, Monoplegia following, 603
- Carter, John R., Generalized capillary and arteriolar platelet thrombosis, 585
- Chambers, William N., Blood pressure studies in 100 cases of coronary occlusion with myocardial infarction, 40
- Chemical structure and antithyroid effect, Further studies on the correlation of, 198
- Cholecystitis, Electrocardiographic observations in chronic, before and after surgery, 598
- Christian, Henry A., *see* Duncan, Garfield G., 53
- Circulatory factors, The effect of, on the bromsulphalein test in liver disease, 470
- Clark, E. Gurney, Maxwell, R. W., and Scott, Virgil, The serologic response following penicillin therapy for early syphilis, 535
- Clark, Thomas E., *see* Kissane, R. W., 410
- Clotting mechanism, Postpartum blood, its, and relationship to the peripheral blood picture, 463
- Cogswell, Robert C., *see* Henderson, Charles R., 488
- Congo red test, Diagnosis of generalized amyloidosis by the: definite diagnostic criteria, 719
- Corcoran, A. C., *see* Taylor, R. D., 475
- Coronary occlusion, Blood pressure studies in 100 cases of, with myocardial infarction, 40
- Curnen, Edward C., *see* Ziegler, James E., 268
- Dickstein, Benjamin, and Wolman, Irving J., Sickle cell anemia, Recent progress of pediatric interest, 728
- Dicumarol, Experiences with penicillin and, in the treatment of subacute bacterial endocarditis, 300
- Dietz, Catherine C., *see* Bondi, Amadeo, Jr., 221
- Dimethylaminoethyl benzhydryl ether hydrochloride (benadryl), Some pharmacologic and clinical experiences with, 418
- Dingwall, R. W., *see* Boyd, Eldon M., 549, 557
- Di Palma, Joseph R., *see* Gubner, Richard, 46
- Diphtheria, acute, and the chronic carrier state, Treatment of, with penicillin, 308
- Discombe, George, and Watkinson, Geoffrey, Atypical anemia with spherocytes and target cells coexisting in the blood, 153
- Dowling, Harry F., Rotman-Kavka, Georgine, Hussey, Hugh H., and Hirsh, Harold L., Treatment of pneumococcal pneumonia with oral and intramuscular penicillin, 413
- Ductus, Effect of patent, arteriosus on body growth, 178
- Duncan, Garfield G., Christian, Henry A., Stokes, Joseph, Jr., Rexer, William F., Nicholson, Joseph T., and Edgar A., An evaluation of immune serum globulin as a prophylactic agent against homologous serum hepatitis, 53
- E**
- Ebaugh, Franklin G., and Hoekstra, Clarence S., Psychosomatic relationships in acute anterior poliomyelitis, 115
- Edgar, A., *see* Duncan, Garfield G., 53
- Eichna, Ludwig W., Horvath, Steven M., and Bean, William B., Post-exertional orthostatic hypotension, 641
- Electrocardiographic changes caused by hyperventilation, 342
 observations in chronic cholecystitis before and after surgery, 598
- Elias, Herbert, *see* McGavack, Thomas H., 418
- Encephalopathy, Posthypoglycemic, 206
- Endamaba histolytica* and other protozoa, Treatment of carriers of, with carbarsone, chiniofon and vioform, 608
- Endocarditis, Experiences with penicillin and dicumarol in the treatment of subacute bacterial, 300
- Endocrine origin, Exophthalmos of, 241
 studies, Gynecomastia due to malnutrition, 31
- Engelberg, R., *see* Pirk, Leo A., 593
- Epinephrine, Insensitivity to, in a patient with a functioning tumor of the adrenal medulla, 324
- Etiologic factor in regional enteritis, The rôle of trauma on the small intestine of dogs, 579
- Evans, Barnett, *see* Wolman, Irving J., 477
- Exophthalmos of endocrine origin, 241
- F**
- Fabricant, Noah D., Throat medication and survey of current trends, 502
- Facial hemangioma extending into the hypothalamus, Hypothermia and elevated serum magnesium in a patient with, 562

D

- Daughenbaugh, P. J., *see* Stebbins, R. B., 671
- Decherd, George M., *see* Ruskin, Arthur, 337
- Diabetes insipidus, Renal excretory function and diet in, 441

- Failure of massive salicylate therapy to suppress the inflammatory reaction in rheumatic fever, 482
- Feinberg, Samuel M., and Friedlaender, Sidney, Histamine antagonists. IV. Pyridil-n'-benzyl - dimethylethylenediamine (pyribenzamine) in symptomatic treatment of allergic manifestations, 58
- Femoral bone marrow cells of the albino rat, 456
- Fidler, R. S., *see* Kissane, R. W., 410
- Fine, Ralph, *see* Machella, Thomas E., 81
- Finland, Maxwell, *see* Paine, Tom F., 676
- Flea *versus* rat control in human plague, 362
- Freeman, Norman E., *see* Hodges, Horace H., 226
- Friedlaender, Sidney, *see* Feinberg, Samuel M., 58
- Friedman, Louis L., The diagnosis of pulmonary disease, 97
- Friedman, Nathan B., Lange, Kurt, and Weiner, David, The pathology of experimental frostbite, 61
- Friedemann, Theodore E., *see* Henderson, Charles R., 488
- Frommeyer, Walter B., Jr., and Spies, Tom D., Relative clinical and hematologic effects of concentrated liver extract, synthetic folic acid and synthetic 5-methyl uracil in the treatment of macrocytic anemias in relapse, 135
- Frostbite, The pathology of experimental, 61
- ## G
- Geremia, Albert E., *see* Levine, Samuel A., 385
- Globulin, An evaluation of immune serum, as a prophylactic agent against homologous serum hepatitis, 53
- Gordon, John E., and Knies, Phillip T., Flea *versus* rat control in human plague, 362
- Griffith, John Q., Jr., *see* Pendergrass, Eugene P., 192
- Growth, Effect of patent ductus arteriosus on body, 178
- Gubner, Richard, Di Palma, Joseph R., and Moore, Elizabeth, Specific dynamic action as a means of augmenting peripheral blood flow. Use of aminoacetic acid, 46
- Gynecomastia associated with vitamin deficiency disease, 176
- due to malnutrition.* I. Clinical studies, 19
- II. Endocrine studies, 31
- ## H
- Hall, Byron E., and Watkins, Charles H., Radioactive isotopes in hematologic disturbances and neoplasms, 621
- Harris, T. N., The failure of massive salicylate therapy to suppress the inflammatory reaction in rheumatic fever, 482
- Harris, H. William, *see* Paine, Tom F., 676
- Haymaker, Webb, *see* Sunderman, F. William, 562
- Heart disease, Liver dysfunction in rheumatic, 410
- Heberden's nodes. VI. The effect of nerve injury upon the formation of degenerative joint disease of the fingers, 181
- Hemorrhoids, internal, Injectional treatment of, 350
- Henderson, Charles R., Wheeler, Norman C., Johnson, Howard C., Cogswell, Robert C., Jr., Berryman, George H., Ivy, Andrew C., Friedemann, Theodore E., and Youmans, John B., Changes in personality appraisal associated with a restricted intake of B vitamins and protein, 488
- Hepatitis, An evaluation of immune serum globulin as a prophylactic agent against homologous serum, 53
- infectious: clinical and laboratory features of* 295 cases, 395
- malignant, Studies on,* 257
- Heyman, Albert, The treatment of syphilis of the central nervous system with penicillin, 661
- Hibbs, Ralph E., Gynecomastia associated with vitamin deficiency disease, 176
- Hirsh, Harold L., *see* Dowling, Harry F., 413
- Hirshfeld, John Winslow, *see* Meyer, Frieda L., 160
- Histamine antagonists. IV. Pyridil-n'-benzyl-dimethylethylenediamine (pyribenzamine) in symptomatic treatment of allergic manifestations, 58
- Hodges, Horace H., and Freeman, Norman E., Thrombophlebitis on the medical service of a general hospital, 226
- Hoekstra, Clarence S., *see* Ebaugh, Franklin G., 115
- Hoffman, William S., and Volini, Italo F., Studies in the oral administration of penicillin. I. Assays of various preparations and the determination of the effective therapeutic dose, 513
- II. Results of treatment of pneumococcal lobar pneumonia and other acute infections with several oral penicillin preparations, 520
- Homologous serum hepatitis, An evaluation of immune serum globulin as a prophylactic agent against, 53
- Hoobler, Sibley W., *see* Lyons, Richard H., 315
- Horne, S. F., and Morris, Leslie M., Use of posterior pituitary extract (pituirin) to measure renal function, 68
- Horsfall, Frank L., *see* Ziegler, James E., 268
- Horvath, Steven M., *see* Eichna, Ludwig W., 641
- Humm, Frances D., *see* Klatskin, Gerald, and Salter, William T., 19, 31
- Humphries, Joseph, Complications of mumps, 354
- Hunt, Marjorie L., *see* Lucia, S. P., 686
- Hussey, Hugh H., *see* Dowling, Harry F., 413
- Hyperbilirubinemia due to nicotinic acid, Clinical significance of, 150
- Hypertension, Menopausal: a critical study, 475
- The indications for irradiation of the pituitary gland in patients with arterial, 192
- Hypertensive persons, Clinical studies of the pharmacologic effects of tetraethyl ammonium chloride in, made in an attempt to select patients suitable for lumbar sympathectomy and ganglionectomy, 572
- Hyperventilation, The electrocardiographic changes caused by, 342
- Hypoprothrombinemic action of quinine sulfate, 593
- Hypotension, Post-exertional orthostatic, 641

Hypothermia and elevated serum magnesium in a patient with facial hemangioma extending into the hypothalamus; 562

I

Immune serum globulin, An evaluation of, as a prophylactic agent against homologous serum hepatitis, 53

Infectious hepatitis: clinical and laboratory features of 295 cases, 395

Influenza B, A study of an outbreak of, in Rochester, New York, 129

Irradiation of the pituitary gland, The indications for, in patients with arterial hypertension, 192

Ivy, Andrew C., *see* Henderson, Charles R., 488

J

Jackson, Will W., Further report on the use of bismuth sodium tartrate intravenously in the treatment of 203 additional patients with tularemia, 358

Jaegge, Kenneth, *see* Wolman, Irving J., 477

Johnson, Howard C., *see* Henderson, Charles R., 488

Jones, George M., Posthypoglycemic encephalopathy, 206

K

Karnosh, Louis J., *see* Stecher, Robert M., 181
Kay, Gloria A., *see* Williams, Robert H., 198
Keating, F. Raymond, Jr., Radio-iodine and the thyroid, 628

Kissane, R. W., Fidler, R. S., and Clark, Thomas E., Liver dysfunction in rheumatic heart disease, 410

Klatskin, Gerald, Salter, William T., and Humm, Frances D., Gynecomastia due to malnutrition. I. Clinical studies, 19

Klatskin, Gerald, *see* Salter, William T., 31

Knies, Phillip T., *see* Gordon, John E., 362

Koop, C. Everett, Plasma substitutes, 233

Koteen, Herbert, The present state of trypanamide in syphilotherapy, 611

Kurnick, Nathaniel B., Treatment of pernicious anemia with synthetic *L. casei* factor, 694

L

Lactates, The effect of sodium and potassium, upon the absorption and elimination of microcrystalline sulfadiazine, 557

Landsteiner, Ernest K., and Brown, Hathorn P., Observations on the treatment of carcinoma of the prostate by orchidectomy, 450

Lange, Kurt, *see* Friedman, Nathan B., 61

Lasker, Sigmund, *see* Wolman, Irving J., 477

Leopold, Irving H., *see* Comroe, Julius H., 641
Leukemic myeloblasts, Partial maturation of, following fresh plasma transfusions, 170

Levine, Samuel A., and Geremia, Albert E., Clinical features of patent ductus arteriosus with special reference to cardiac murmurs, 385

Lewis, Lena A., Moses, Jacob, and Schneider, R. W., Plasma proteins. II. Alteration in alloxan diabetic rabbits especially in relation to ocular damage, 214

Liver disease, The effect of circulatory factors on the bromsulphalein test in, 470
dysfunction in rheumatic heart disease: preliminary report, 410

extract, Relative clinical and hematologic effects of concentrated, synthetic folic acid and synthetic 5-methyl uracil in the treatment of macrocytic anemias in relapse, 135

Lowenstein, V. E., *see* Birchall, Robert, 572

Lowry, Charles F., *see* Zimmerman, Hyman J., 395

Lucia, S. P., and Hunt, Marjorie L., The significance of the myeloid maturation curve in material aspirated from the sternal bone marrow, 686

Lymph nodes, Fatal infection with poliomyelitis virus in a laboratory technician. Isolation of virus from, 9

Lyons, Richard H., Moe, Gordon K., Neligh, Rosalie B., Hoobler, Sibley W., Campbell, Kenneth N., Berry, Robert L., and Rennick, Barbara R., The effects of blockade of the autonomic ganglia in man with tetraethylammonium. Preliminary observations on its clinical application, 315

M

Macek, T. J., *see* Stebbins, R. B., 671

Maehella, Thomas E., with Fine, Ralph, and Burgoon, David F., The relationship of bromsulphalein retention to the fever of natural *P. falciparum* malaria, 81

Macrocytic anemias in relapse, Relative clinical and hematologic effects of concentrated liver extract, synthetic folic acid and synthetic 5-methyl uracil in the treatment of, 135

Malaria, *P. falciparum*, The relationship of bromsulphalein retention to the fever of natural, 81

Malnutrition, Gynecomastia due to, 19, 31

Marfori, L., Stefanini, M., and Bramante, P., Clinical significance of hyperbilirubinemia due to nicotinic acid, 150

Martens, T. G., Exophthalmos of endocrine origin, 241

Maxwell, R. W., *see* Clark, E. Gurney, 535

Maycock, Robert L., and Rose, Edward, Insensitivity to epinephrine in a patient with a functioning tumor of the adrenal medulla, 324

McConnell, Jeannette, *see* Rose, Edward, 74

McGavack, Thomas H., Elias, Herbert, and Boyd, Linn J., Some pharmacologic and clinical experiences with dimethylaminoethyl benzhydryl ether hydrochloride (henadryl), 418

Menopausal hypertension: a critical study, 475

Meyer, Frieda L., Hirshfeld, John Winslow, Abbot, William E., Pilling, Matthew A., Williams, Harold H., and Richards, Allen J., Nitrogen balance and blood volume studies in man during and following repeated plasma transfusions, 160

Meyer, Ovid O., *see* Thill, Charles J., 300

Migrainous personality and constitution. The essential features of the disease: a study of 500 cases, 1

Mirick, George S., *see* Ziegler, James E., 268

Moe, Gordon K., *see* Lyons, Richard H., 315

Molina, Richard D., Santos, Hermogenes, A., and Alimurung, Mariano M., The intravenous use of human ascitic fluid in shock, nephrosis and allied conditions, 435

Monoplegia following carotid sinus pressure in the aged, 603

Moore, Elizabeth, *see* Gubner, Richard, 46

Morris, Leslie M., *see* Horne, S. F., 68

Moses, Jacob, *see* Lewis, Lena A., 214

Mumps, Amylase levels during: The findings in blood and saliva, 477

Complications of, 354

Murray, Roderick, *see* Paine, Tom F., 676

Myeloid maturation curve, The significance of the, in material aspirated from the sternal bone marrow, 686

Myeloma of bone, The changing concept of, 282

Myocardial infarction, Blood pressure studies in 100 cases of coronary occlusion with, 40

N

Neligh, Rosalie B., *see* Lyons, Richard H., 315

Nephrosis and allied conditions, Intravenous use of human ascitic fluid in shock, 435

Nicholson, Joseph T., *see* Duncan, Garfield G., 53

Nicotinic acid, Clinical significance of hyperbilirubinemia due to, 150

Nitrogen balance and blood volume studies in man during and following repeated plasma transfusions, 160

O

Ochsner, Alton, *see* Spellberg, M. A., 579

Ocular damage, Alteration in alloxan diabetic rabbits especially in relation to, 214

Odell, Lester D., Renal filtration rates in pregnancy toxemia. Inulin and exogenous creatinine, 709

Orchidectomy, Observations on the treatment of carcinoma of the prostate by, 460

Orthostatic hypotension, Post-exertional, 641

P

Padis, Nicholas, *see* Pendergrass, Eugene P., 192

Page, Ernest W., Plasma angiotonase concentration in normal and toxemic pregnancies, 715

Page, Irvine H., *see* Birchall, Robert, 572

Page, Irvine H., *see* Taylor, R. D., 475

Paine, Tom F., Murray, Roderick, Harris, H. William, and Finland, Maxwell, Streptomycin in the treatment of certain gram-negative bacillus infections of the central nervous system, 676

Pancreas, Disseminated calcification of the, 290

Pancreatitis, Subacute and chronic: Disseminated calcification of the pancreas, 290

Patent ductus arteriosus, Clinical features of, with special reference to cardiac murmurs, 385

The Effect of, on body growth, 178

Pathology of experimental frostbite, 61

Paul, John R., *see* Wenner, Herbert A., 9

Pendergrass, Eugene P., Griffith, John Q., Jr., Padis, Nicholas, and Barden, Robert P., The indications for irradiation of the pituitary gland in patients with arterial hypertension, 192

Penicillin and dicumarol, Experiences with, in the treatment of subacute bacterial endocarditis, 300

and other antibiotics, A routine method for the rapid determination of susceptibility to, 221

Studies in the oral administration of, 513, 520 therapy, Serologic response following, for early syphilis, 535

The oral administration of, in dogs, 671

The treatment of acute diphtheria and the chronic carrier state with, 308

The treatment of syphilis of the central nervous system with, 661

Treatment of pneumococcic pneumonia with oral and intramuscular, 413

Peripheral blood flow, Specific dynamic action as a means of augmenting, Use of aminoacetic acid, 46

Perlmutter, Martin, *see* Stadie, William C., 655

Personality and constitution, The migrainous. The essential features of the disease: a study of 500 cases, 1

appraisal, Changes in, associated with a restricted intake of B vitamins and protein, 488

repercussions of anterior poliomyelitis, a review of the literature, 109

Pilling, Matthew A., *see* Meyer, Frieda L., 160

Pirk, Leo A., and Engelberg, R., Hypoprothrombinemic action of quinine sulfate, 593

Pituitary gland, The indications for irradiation of the, in patients with arterial hypertension, 192

posterior, extract (puitritin), Use of, to measure renal function, 68

Plague, Flea *versus* rat control in human, 362

Plasma angiotonase concentration in normal and toxemic pregnancies, 715

proteins. II. Alteration in alloxan diabetic rabbits especially in relation to ocular damage, 214

substitutes, 233

transfusions, Nitrogen balance and blood volume studies in man during and following repeated, 160

Partial maturation of leukemic myeloblasts following fresh, 170

Pneumococcic lobar pneumonia and other acute infections, Results of treatment of, with several oral penicillin preparations, 520

pneumonia, Treatment of, with oral and intramuscular penicillin, 413

Poliakoff, Harvey, Mild rheumatic reaction in coast guard recruits, 37

Poliomyelitis, acute anterior, Psychosomatic relationships in, 115

anterior, Personality repercussions of, a review of the literature, 109

virus, Fatal infection with, in a laboratory technician. Isolation of virus from lymph nodes, 9

- Porter, William B., The effect of patent ductus arteriosus on body growth, 178
- Posthypoglycemic encephalopathy. Case Reports, 206
- Postpartum blood: its clotting mechanism and relationship to the peripheral blood picture, 463
- Pregnancies, normal and toxemic, Plasma angiotensinase concentration in, 715
- Pregnancy toxemia, Renal filtration rates in. Inulin and exogenous creatinine, 709
- Prostate, Observations on the treatment of carcinoma of the, by orchidectomy, 450
- Protozoa, Treatment of carriers of *Endamaba histolytica* and other, with carbarsone, chiniofon and vioform, 608
- Pulmonary disease, The diagnosis of, 97
- Psychosomatic relationships in acute anterior poliomyelitis, 115

Q

- Quinine sulfate, Hypoprothrombinemic action of quinine sulfate, 593

R

- Radioactive isotopes in hematologic disturbances and neoplasms, 621
- Radio-iodine and the thyroid, 628
- Reactivity, Increased, caused by adrenalin, 331
- Regional enteritis, The rôle of trauma as a possible etiologic factor in The effect of non-penetrating trauma on the small intestine of dogs, 579
- Reiser, Raymond, *see* Zimmerman, Hyman J., 395
- Renal excretory function and diet in diabetes insipidus, 441
- filtration rates in pregnancy toxemia. Inulin and exogenous creatinine, 709
- function, Use of posterior pituitary extract (pituitrin) to measure, 68
- Rennick, Barbara R., *see* Lyons, Richard H., 315
- Respiratory tract infections, acute, Diagnosis of, 268

Reviews (Reviewer's initials in parentheses):

- Abramowitch D., Treatment by Ion Transfer (S H.), 758
- Albrecht, F. Kenneth, Modern Management in Clinical Medicine (R K.), 756
- Allen, Raymond B., Medical Education and the Changing Order (I S.), 512
- Banai, Andrew Ladislaus, Pneumoperitoneum Treatment (H C.), 381
- Beaver, William C., General Biology (M McC.), 511
- Bedford, T., Environmental Wornth and Its Measurement (W S.), 512
- Braun-Menendez, Eduardo, Fascioli, Juan Carlos Lelup, Luis F., Munoz Juan M., and Taquini, Alberto C., Renal Hypertension (I P.), 511
- Cameron, A. T., Recent Advances in Endocrinology (I Z.), 511
- Collens, William S., The Modern Treatment of Diabetes Mellitus (F. L.), 383
- Curran, Desmond, Psychological Medicine (N Y.), 254
- Derbes, Vincent J., The Treatment of Bronchial Asthma (R K.), 757
- Evans, C. Lovatt, Starling's Principles of Human Physiology (M J.), 125
- Friedenwald, Harry, Jewish Luminaries in Medical History (H B.), 256
- Gold, Harry, *et al.*, Cornell Conferences on Therapy (H H.), 127

Reviews (Reviewer's initials in parentheses):

- Graybiel, Ashton, and White, Paul D., Electrocardiography in Practice (C. W.), 511
- Guthrie, Douglas, History of Medicine (F P.), 380, (E. L.), 759
- Haden, Russell L., Principles of Hematology (E T.), 256
- Harris, I., Studies in Hypertony and the Prevention of Disease (J G.), 234
- Harrison, Shelby M., and Andrews, F. Emerson, American Foundations for Social Welfare (W S.), 125
- Held, I. W., Peptic Ulcer (J N.), 381
- Hennessey, Thomas Francis, Vocational and Professional Monographs—Psychotherapy (G P.), 758
- Hoskins, R. G., The Biology of Schizophrenia (N Y.), 252
- Hume, Edward H., Doctors East, Doctors West (E K.), 382
- Ivy, Robert H., and Curtis, Lawrence, Fractures of the Jaws (H R.), 126
- John, Henry J., Diabetes (F L.), 383
- Katz, Louis N., Electrocardiography (W J.), 126
- Kirk, Esben, Acidosis (J A.), 757
- Kisch, Bruno Stroppanthin (J C., Jr.), 382
- Macy, Icie G., Nutrition and Chemical Growth in Childhood, Vol. II (E T.), 250
- Mam, Roland J., Synopsis of Physiology (H B.), 251
- Medical Clinics of North America, Mayo Clinic, July 1946 (J H.), 255
- Medical Clinics of North America, New York Number, May 1946, Rheumatic Disease (C F.), 759
- Mennell, James B., Physical Treatment by Movement, Manipulation and Massage (S H.), 125
- Movitt, Eli Rodin, Digitalis and Other Cardiotonic Drugs (C. W.), 252
- Newcomer, H. Sidney, Editor, Curare Intocostrin (C L.), 380
- Peters, John P., Quantitative Chemical Chemistry, Interpretations (J. A.), 757
- Selling, Lowell S., Synopsis of Neuropsychiatry (J S.), 251
- Sheehan J. Eastman, General and Plastic Surgery (H R.), 126
- Sherrington, Sir Charles, The Endeavor of Jean Fernel (E K.), 383
- Sjostedt, Sven, Pathogenicity of Certain Serological Types of B. coli (P E.), 756
- Smilie Wilson G., Preventive Medicine and Public Health (A H.), 250
- Smith, Geddes, Psychotherapy in General Practice (N Y.), 255
- Spiegel, E. A., Progress in Neurology and Psychiatry (N Y.), 254
- Stern, Bernhard J., Medicine in Industry (A H.), 253
- Stone, Moses J., Diagnosis and Treatment of Pulmonary Tuberculosis (S S.), 252
- Underwood, E. Ashworth, Manual of Tuberculosis (E L.), 255
- Urbach, Erich, Skin Diseases, Nutrition and Metabolism (R G.), 384
- Wesson, Miley B., Urologic Roentgenology (C P.), 381
- Whitby, Sir Lionel E. H., Disorders of the Blood (W W.), 382

- Rever, William F., *see* Duncan, Garfield G., 53
- Rheumatic fever, The failure of massive salicylate therapy to suppress the inflammatory reaction in, 482
- heart disease, Liver dysfunction in, 410
- reaction, Mild, in coast guard recruits, 37
- Rheumatoid arthritis. IV. Hemolytic streptococcus precipitin reactions, 87
- V. The agglutination of hemolytic streptococci, 94
- Richards, Allen J., *see* Meyer, Frieda L., 160
- Robbins, Robert, *see* Aegerter, Ernest, 282
- Robinson, David, *see* Stadie, William C., 655
- Rose, Edward, and McConnell, Jeannette, Thiouracil in thyrotoxicosis. Results of prolonged treatment in 35 cases, 74
- Rose, Edward, *see* Maycock, Robert L., 324
- Rotman-Kavka, Georgine, *see* Dowling, Harry F., 413

Ruskin, Arthur, and Decherd, George M., Jr.,
Thiamine circulation time, 337

S

Salicylate therapy, The failure of massive, to
suppress the inflammatory reaction in rheu-
matic fever, 482

Salter, William T., Klatskin, Gerald, and
Humm, Frances D., Gynecomastia due to
malnutrition. II. Endocrine studies, 31

Salter, William T., *see* Klatskin, Gerald, 19

Santos, Hermogenes, A., *see* Molina, Richard D.,
435

Scherf, David, and Schlachman, Milton, The
electrocardiographic changes caused by hy-
perventilation, 342

Schlachman, Milton, *see* Scherf, David, 342

Schloss, Eugene M., *see* Blumberg, Nathan, 470

Schneider, R. W., *see* Lewis, Lena A., 214

Schwind, Joseph L., Partial maturation of leu-
kemic myeloblasts following fresh plasma
transfusions, 170

Scott, Virgil, *see* Clark, E. Gurney, 535

Selikoff, Irving J., Diagnosis of generalized amy-
loidosis by the Congo red test: definitive
diagnostic criteria, 719

Serologic response following penicillin therapy
for early syphilis, 535

Sheppard, Siegal, *see* Zeman, Frederic D., 603

Shock, nephrosis and allied conditions, The
intravenous one of human ascitic fluid in, 435

Sickle cell anemia, Recent progress of pediatric
interest, 728

Slavin, Howard B., *see* Bruce, Robert A., 129

Smith, Dorothy E., *see* Bondi, Amadeo, Jr., 221

Snape, William J., *see* Wirts, C. Wilmer, 290

Solomon, Babette, *see* Williams, Robert H., 198

Spaulding, Earle H., *see* Bondi, Amadeo, Jr.,
221

Specific dynamic action as a means of augment-
ing peripheral blood flow. Use of aminoacetic
acid, 46

Spellberg, M. A., and Ochsner, Alton, The rôle
of trauma as a possible etiologic factor in
regional enteritis. The effect of non-penetrat-
ing trauma on the small intestine of dogs, 579

Spherocytes and target cells coexisting in the
blood, Atypical anemia with, 153

Spies, Tom D., *see* Frommeyer, Walter B., Jr.,
135

Stadie, William C., Perlmutter, Martin, and
Robinson, David, The tyrosinase inhibiting
action of serum from normal and cancerous
patients, 655

Stanfield, Clyde E., Personality repercussions of
anterior poliomyelitis, a review of the litera-
ture, 109

Stebbins, R. B., Maeck, T. J., and Daughen-
baugh, P. J., The oral administration of peni-
cillin in dogs, 671

Stecher, Robert M., and Karnosh, Louis J.,
Heberden's nodes. VI. The effect of nerve
injury upon the formation of degenerative
joint disease of the fingers, 181

Stefanini, M., *see* Marfori, L., 150

Stokes, John H., and Beerman, Herman, Virus
pyrogen and virus pyrogen photosensitivity
relationships in cutaneous disease, 494

Stokes, Joseph, Jr., *see* Duncan, Garfield G., 53

Streptococci, hemolytic. Agglutination of.
Rheumatoid arthritis, V., 94

Precipitin reactions. Rheumatoid arthritis,
IV, 87

Streptomycin in the treatment of certain gram-
negative bacillus infections of the central
nervous system, 676

Sulfadiazine, The absorption and elimination of,
administered as tablets, as a ground (micro-
nized) powder and as microcrystals, 549

The effect of sodium and potassium lactates
upon the absorption and elimination of
microcrystalline, 557

Sunderman, F. William, and Haymaker, Webb,
Hypothermia and elevated serum magnesium
in a patient with facial hemangioma extend-
ing into the hypothalamus, 562

Sympathectomy and ganglionectomy, Clinical
studies of the pharmacologic effects of tetra-
ethyl ammonium chloride in hypertensive
persons made in an attempt to select patients
suitable for lumbodorsal, 572

Syphilis of the central nervous system, The
treatment of, with penicillin, 661

Serologic response following penicillin therapy
for early, 535

Syphilotherapy, The present status of trypara-
mide in, 611

T

Target cells, Atypical anemia with spherocytes
and, coexisting in the blood, 153

Taylor, R. D., Corcoran, A. C., and Page,
Irvine H., Menopausal hypertension: a criti-
cal study, 475

Taylor, R. D., *see* Birchall, Robert, 572

Tetraethyl ammonium chloride, Clinical studies
of the pharmacologic effects of, in hyperten-
sive persons made in an attempt to select
patients suitable for lumbodorsal sympath-
ectomy and ganglionectomy, 572

Tetraethyl ammonium, The effects of blockade
of the autonomic ganglia in man with. Pre-
liminary observations on its clinical applica-
tion, 315

Thiamine circulation time, 337

Thill, Charles J., and Meyer, Ovid O., Experi-
ences with penicillin and dicumarol in the
treatment of subacute bacterial endocarditis,
300

Thiouracil in thyrotoxicosis. Results of pro-
longed treatment in 35 cases, 74

Throat medication: a survey of current trends,
502

Thrombophlebitis on the medical service of a
general hospital, 226

Thrombosis, Generalized capillary and arteriolar
platelet, 585

Thyroid, Radio-iodine and the, 628

Thyrotoxicosis, Thiouracil in. Results of pro-
longed treatment in 35 cases, 74

Treatment, injectional, of internal hemorrhoids,
350

of acute diphtheria and the chronic carrier
state with penicillin, 308

of carriers of *Endamaba histolytica* and other
protozoa with carbarsone, chiniofon and
vioform, 608

Treatment of internal hemorrhoids, Injectional, 350

of macrocytic anemias in relapse, Relative clinical and hematologic effects of concentrated liver extract, synthetic folic acid and synthetic 5-methyl uracil in the, 135

of pernicious anemia with synthetic *L. casei* factor, 694

of pneumococcic pneumonia with oral and intramuscular penicillin, 413

of subacute bacterial endocarditis, Experiences with penicillin and dicumarol in the, 300

of syphilis of the central nervous system with penicillin, 661

Trauma, The rôle of, as a possible etiologic factor in regional enteritis. The effect of non-penetrating trauma on the small intestine of dogs, 579

Tryparsamide in syphilotherapy, The present status of, 611

Tularemia, Further report on the use of bismuth sodium tartrate intravenously in the treatment of 203 additional patients with, 358

Tumor, functioning, of the adrenal medulla, Insensitivity to epinephrine in a patient with, 324

Turell, Robert, Injectional treatment of internal hemorrhoids, 350

Tyrosinase inhibiting action of serum from normal and cancerous patients, 655

U

Ueyama, Kahn, *see* Zimmerman, Hyman J., 395

V

Vagina, The, 737

Virus from lymph nodes, Isolation of. Fatal infection with poliomyelitis virus in a laboratory technician, 9

pyogen and virus pyogen photosensitivity relationships in cutaneous disease, 494

Vitamin deficiency disease, Gynecomastia associated with, 176

Vogel, Mildred, The femoral bone marrow cells of the albino rat, 456

Volini, Italo F., *see* Hoffman, William S., 510,

W

Wallis, Allan D., Rheumatoid arthritis. IV. Hemolytic streptococcus precipitin reactions, 87

V. The agglutination of hemolytic streptococci, 94

Watkins, Charles H., *see* Hall, Byron E., 621

Watkinson, Geoffrey, *see* Discombe, George, 153

Weiner, David, *see* Friedman, Nathan B., 61

Weinstein, Louis, The treatment of acute diphtheria and the chronic carrier state with penicillin, 308

Wenner, Herbert A., and Paul, John R., Fatal infection with poliomyelitis virus in a laboratory technician. Isolation of virus from lymph nodes, 9

Wheeler, Norman C., *see* Henderson, Charles R., 488

Williams, Harold H., *see* Meyer, Frieda L., 160

Williams, Robert H., and Kay, Gloria A., Assisted by Solomon, Babette, Further studies on the correlation of chemical structure and antithyroid effect, 198

Wirts, C. Wilmer, and Snape, William J., Disseminated calcification of the pancreas: Subacute and chronic pancreatitis, 290

Wolman, Irving J., Evans, Barnett, Lasker, Sigmund, and Jaegge, Kenneth, Amylase levels during mumps: The findings in blood and saliva, 477

Wolman, Irving J., *see* Dickstein, Benjamin, 728

Y

Youtmans, John B., *see* Henderson, Charles R., 488

Z

Zeman, Frederic D., and Siegal, Sheppard, Monoplegia following carotid sinus pressure in the aged, 603

Ziegler, James E., Curnen, Edward C., Mirick, George S., and Horsfall, Frank L., Diagnosis of acute respiratory tract infections, 268

Zimmerman, Hyman J., Lowry, Charles F., Ueyama, Kahn, and Reiser, Raymond, Infectious hepatitis: clinical and laboratory features of 295 cases, 395

